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No. 6 JANUARY 31, 1916

TORULA INFECTION IN MAN

A GROUP OF CASES, CHARACTERIZED BY CHRONIC LESIONS OF THE CENTRAL NERVOUS SYSTEM, WITH CLINICAL SYMPTOMS SUGGESTIVE OF CEREBRAL TUMOR, PRODUCED BY AN ORGANISM BELONGING TO THE TORULA GROUP (TORULA HISTOLYTICA, N. SP.)

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By

JAMES L. STODDARD, M.D., AND ELLIOTT C. CUTLER, M.D.

NEW YORK
1916

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MONOGRAPH OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH, NO. 6.
JANUARY 31, 1916.

TORULA INFECTION IN MAN.

A Group of Cases, Characterized by Chronic Lesions of the Central Nervous System, with Clinical Symptoms Suggestive of Cerebral Tumor, Produced by an Organism Belonging to the Torula Group (Torula histolytica, N. Sp.).*

By JAMES L. STODDARD, M.D., and ELLIOTT C. CUTLER, M.D.

(From the Pathological Laboratory and Surgical Service of the Peter Bent Brigham Hospital, Boston.)

Plates 1 to 9.

(Received for publication, June 14, 1915.)

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I. INTRODUCTION.

Two cases from the clinic of Dr. Harvey Cushing, at the Peter Bent Brigham Hospital, presented at autopsy unusual lesions in the brain and meninges. The histories and physical examinations included such signs of cerebral tumor as to indicate decompression or exploratory operation, but the pathological examination in each case proved the complete absence of tumor. Lesions were found, however, which fully explained the clinical symptoms and physical signs. Enormous numbers of organisms having many points of resemblance to those of blastomycosis occurred in all of the lesions in such a manner as to leave no doubt of their causal relations. Certain differences from the usual descriptions of the organisms of the blastomycosis group and their lesions made a careful study necessary to determine the relations of our cases.

Two problems which have received increasing attention in late years, without great progress toward their solution, were thus brought to our notice by the study of the cases,—the problem of cerebral pseudotumor, and the problem of the relationships of the lower fungi forming the group called blastomycosis. It seemed probable that our cases might throw light upon both these questions.

In the study of the first problem, that of pseudotumor cerebri, the literature furnished a considerable number of cases in which symptoms and signs of brain tumor existed for a short or long time, with subsequent recovery, or with indefinite autopsy findings. The cases were mysterious, but many reports by competent observers left no doubt of their existence. No well known disease could explain them; the promise of their solution lay in the finding of similar cases fully studied and made clear, or in the investigation of little known disease capable of producing such syndromes. To show that our cases and experiments suggest a solution is part of the object of this paper.

In trying to solve the other problem, that of the relationships of the organisms of the blastomycosis group, we studied the literature and made animal experiments. We used in our experiments pure cultures of three different organisms: one isolated from a human case of cutaneous blastomycosis, one from a human case of coccidioidal granuloma, and one from Dr. Frothingham's case of torula infection in a horse. Inoculations were made in various ways upon several species of laboratory animals, and agglutination experiments done upon the infected animals. We realized that a great deal of work had been done upon the cultural characteristics of these organisms, but hoped that the careful study of the histological changes and the serological reactions would give more definite information as to the similarity or identity of the diseases produced.

Wolbach says, in regard to the blastomycotic group of organisms:

> For the present we wish to emphasize the necessity for careful studies upon the organisms by means of animal experiments, for it is by this method only that the more striking differences between the types may be demonstrated. Cultural methods as applied to bacteria have not been of value to us.

It is difficult, and often impossible, to make fungi produce a characteristic fructification. None has yet been discovered for the group of organisms causing the cases of blastomycosis localized near Chicago.

In our second case cultures of the ventricular fluid made in bouillon were injected into mice intraperitoneally, and at autopsy a meningitis was found with organisms like those in the human meninges. In the first case no spinal fluid was obtained on account of the danger of puncture during pressure symptoms, and the technique of formalin injection of the brain before removal prevented cultures at autopsy.

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The lesions were so peculiar, however, that when we succeeded in reproducing them in animals no doubt remained of their identity with the experimental ones.

As the study of our cases and experimental results progressed, we found that another problem of importance came into relation with our work. It is recognized that lesions similar to those of tuberculosis occur in other diseases; coccidioidal granuloma, for instance, has often very similar lesions, but the parasite is so large that its recognition is not difficult; blastomycosis occasionally produces tubercle-like nodules; other fungi are known to produce reactions more or less closely similar to tuberculosis. We found in our cases and in our experimental work lesions so closely resembling tuberculosis that a differential diagnosis would be impossible without finding the parasites. The parasites are so small that they could easily be overlooked, and in the later stages of the lesions they disappear entirely, leaving as a result tubercle-like nodules with no trace of their origin. The lesions have typical caseation or consist of miliary nodules without caseation. A number of human cases with similar lesions in which no tubercle bacilli could be found have come to our attention in this hospital. It is possible that many cases diagnosed as tuberculosis may be due to this organism.

II. HISTORICAL.

An enormous mass of literature has grown up with reference to lesions in human beings, produced by organisms which bud without producing mycelium in the tissues, and by some that are roughly similar, but that do not bud in the tissues. All of these have been loosely classified as cases of blastomycosis. As many observers long ago realized, there is nothing distinctive about the budding type of growth, for many fungi higher than yeasts have a stage in which they reproduce by budding.

1. Evidence That Coccidioidal Granuloma Is Distinct from the Other Diseases Called Blastomycosis.

It seemed possible, therefore, that the name blastomycosis would eventually be applied to a group of diseases produced by various organisms. This has proved to be the case, for at least two distinct types have been separated by different observers. They are the coccidioidal granuloma and the blastomycosis types. The difference is simple; the coccidioidal organism never buds in tissue but sporulates; the blastomycotic organism buds but never sporulates. It is obvious that coccidioidal granuloma should never have been confused with blastomycosis. There are further differences. Thus the coccidioidal organism varies more in size, having large forms up to 30 to 40μ in diameter, which produce many small ascospores which escape from the capsule. The coccidioidal organism, furthermore, produces lesions more nearly like tuberculosis, and the infection more often spreads by the lymphatics as well as by the blood. The disease is almost invariably fatal (Wolbach, however, reports a case with recovery) and occurs practically always in males who have lived in the San Joaquin valley, California. Cases of blastomycosis have a wider distribution, the systemic cases recover in 10 per cent of the instances recorded, and cutaneous cases frequently recover without internal lesions. The patients are benefited, as a rule, by iodides, which have no effect on coccidioidal granuloma.

Among German observers, Buschke does not recognize a difference between the coccidioidal and the blastomycotic type, and confuses coccidioidal granuloma with coccidiosis. Wright regards them as different manifestations of the same disease. Ever since the first observations by Posadas and Wernicke, and Rixford and Gilchrist, evidence has accumulated that the diseases are really distinct. Wolbach accurately described the life cycle of the organism of dermatitis coccidioides, and found it entirely different from that of blastomycosis; MacNeal and Taylor studied the life cycle of the coccidioides organism, summarized the known cases, and concluded that the two diseases were distinct clinically, pathologically, and biologically. Other summaries of the literature by Ophüls, Ryfkogel, and Hektoen lead to the same conclusion Innumerable studies of the organism of blastomycosis have never revealed the methods of reproduction by endosporulation characteristic of the coccidioidal type. A possible source of confusion in the early accounts was the occurrence, in apposition, of small forms in coccidioidal granuloma, which simulated buds. True budding is not found in coccidioidal granuloma, but is constant in blastomycosis. A recent paper by Brown and Cummins again establishes the differences between the two diseases and adds evidence from animal experiments.

The first study of our cases with the many budding forms showed that the picture was entirely different from that of coccidioidal granuloma. Our experiments substantiated the statements made by the other workers as to the differences in the two diseases, and showed us that the brain lesions we produced with *Coccidioides immitis* were different in type from those of our cases.

2. Previous Attempts to Classify the Blastomycoses.

Of the remaining group of true blastomycoses, many attempts by American workers to make divisions have resulted in indefinite conclusions. Ricketts, in his extensive study of organisms from seventeen cases of cutaneous blastomycosis, made a tentative division into blastomycetoid, or organisms showing a predominating tendency to bud, oidiomycetoid, or those showing a tendency to bud or produce mycelium, and hyphomycetoid, or organisms tending to produce aerial hyphæ. The differences were somewhat inconstant and of degree rather than of kind. Hamburger studied organisms from four cases of systemic infection, and found them practically identical. Montgomery and Ormsby have asserted that all types hitherto described have been observed at different times in the same strain. Stober states that in his study of eleven strains the chief difference was in the size of mycelium and spores. In all the organisms studied mycelium production has occurred sooner or later; it is favored by room temperature, dryness of the medium, and transplantation, while budding occurs chiefly when there is abundant moisture and a thermostat temperature.

Of German workers, Buschke divides the blastomycoses into diseases produced by true yeasts, saccharomycoses, and those produced by organisms which bud and produce mycelium, the oidiomycoses. Two cases of true yeast infection in man are sufficiently well established to deserve attention.

When we turn to botanical literature we find that there is a distinction between the true yeasts and the torulæ (or yeast-like organisms which do not produce endospores) on the one hand, and the oidium group on the other hand, in which both budding and hypha production occur. The organisms of ordinary blastomycosis evidently belong to the oidium group.

In animal experiments with lower fungi, it was observed that the torulæ had marked pathogenic powers for animals,—greater than those of yeasts. Rabinowitsch, in an investigation of forty species of yeast, found only eight pathogenic. Klein found a pathogenic torula in milk, and produced lesions in animals with a pure culture; Cohn worked with the same organisms and obtained similar results. Nichols, in his experiments upon budding organisms in relation to cancer, used two strains of torula and easily produced lesions. Many other workers have confirmed these statements. Often a tendency for the organisms to produce brain lesions is noted. Frothingham found a torula naturally producing lesions in a horse, and in animal experiments proved its marked pathogenic powers. It was possible, then, that an organism pathogenic for animals would sooner or later be found to produce disease in man. We could not find, however, cases reported as torula infection.

In studying the organisms of the cases of blastomycosis, it seemed of value to look up the literature, first from the point of view of brain lesions, and to tabulate all the cases classified as blastomycosis which involved the brain, and then to look for cases like ours and for atypical cases; secondly, to tabulate the cases of systemic blastomycosis without brain lesions, and observe similarities and differences.

The results of our tabulations show that the cases of systemic blastomycosis without brain lesions are closely alike clinically and pathologically, but there are divisions to be made within this group, as will be explained in detail in the discussion of the cases.

The cases with brain lesions, on the contrary, are a much less homogeneous group. A number of cases stand out from the rest as distinctly atypical, but similar to each other.

3. *Cases of Systemic Blastomycosis with Brain Lesions.*

A. Abstracts of Ten Cases.

Case 1.—Reported by von Hansemann.

Patient.—A laborer, 18 years old, with tuberculosis of the lungs (bacilli in sputum).

Present Illness.—Onset with apathy. Double abducens paralysis, vertical nystagmus, unequal pupils, choked disc, slow pulse (46). Spinal puncture gave at first a watery, later a slightly cloudy fluid, in which were at first few, then more numerous lymphocytes, but always peculiar large round bodies considered to be corpora amylacea. They were in part singly, in part doubly contoured, of very variable size, some larger, some smaller than an erythrocyte, were colorless and moderately refractive. There were also biscuit forms, and longer forms in three to four jointed figures that recalled myelin drops. Cultures did not grow.

Diagnosis.—Tubercular meningitis.

Course.—Then followed vomiting, involuntary discharge of feces and urine, delirium, and coma, and death 19 days after entrance.

Autopsy.—Tuberculosis of the lungs. The pia and arachnoid were saturated and the ventricles filled with a slightly cloudy fluid containing bodies similar to those described above. On the surface of the brain were about sixty small cysts, the largest the size of a hemp-seed, only slightly projecting above the surface, and on section emptying themselves partially, leaving slimy colloidal masses. Section showed similar cysts, often confluent, especially numerous in the corpus striatum and its neighborhood. The corpus striatum and part of the thalamus bulged out into the lateral ventricle with a myxomatous-like mass. Cultures did not grow.

Microscopical Examination.—Cysts and tumor-like masses consisted of enormous collections of yeast-like bodies embedded in a colloid-like substance, and the surrounding brain substance showed very little reaction. In many colonies were numerous large phagocytic cells, but for the most part the organisms lay free. In the pia was a slight increase in lymphocytes and leukocytes, especially the former, but the numerous organisms called forth almost no reaction of the meningeal tissues.

Case 2.—Reported by Türck.

Patient.—A woman, 43 years old, servant, entered the hospital on Apr. 21, 1906.

Past History.—Scarlet fever in childhood; epilepsy with general convulsions since the age of 4 years; operation for purulent neck glands at 11; later an operation for eye trouble. In recent years much coughing, but no hemoptysis.

Present Illness.—A sudden onset at the end of March, 1906, with headache, vomiting, and a chill. There followed weakness, frequent nocturnal or early morning vomiting, and increasing stiffness of the neck.

Examination.—Apr. 21. A slight, poorly nourished woman; temperature 38° to 38.2°C. Frontal and occipital headache; cranial tenderness, and tenderness of the stiff cervical, thoracic, and lumbar spinal muscles; general hyperesthesia toward pin pricks, but no sensitiveness of the abdominal or leg muscles; positive Kernig; normal knee jerk; throat normal; scars on neck; palpable glands in the neck and axilla; lungs with dulness at the apices, with râles and bronchial breathing; no sputum; urine with much nucleo-albumin and mucin, and a trace of serum albumin.

Course.—No marked change. No cranial nerve involvement. Temperature irregular, 37° to 38°C., pulse 80. Lumbar puncture on Apr. 25 gave a clear serous fluid under increased pressure. At the end of 4 weeks the condition of the patient was the same as at entrance. This caused doubt as to the diagnosis of tubercular meningitis, which was made on entrance. A second lumbar puncture on May 3 gave 5 cc. under high pressure. The fluid was slightly cloudy.

Microscopical Examination.—Many typical yeasts of round or oval shape. The extraordinary finding made a verification necessary and a second puncture was done with especial care on May 5. The specific gravity of the fluid was 1,008. A slight clot formed on standing. No tubercle bacilli were found, but there were enormous numbers of organisms often joined as are yeast cells, numerous small lymphocytes, rare red cells, and groups of large phagocytic mononuclear cells. On May 8 examination showed great emaciation; otherwise no change.

Blood Examination.—Red cells 5,210,000; hemoglobin 14.49 per cent (Fleischer-Miescher); white cells 7,000; increased blood platelets.

Differential Count.—Polymorphonuclears 91.5 per cent; lymphocytes 3.6 per cent; large mononuclears 4.9 per cent.

On May 10 an increasing white coat over the throat was noticed. The general condition grew worse. Lumbar punctures on May 13, 14, and 15 gave results similar to the earlier ones. On May 15 the temperature rose to 40.1°C. and the patient died.

Autopsy.—Dura thin and smooth; a soft brain with slightly cloudy hydrocephalus, and cloudy edema of the meninges of the Sylvian fissure. The mucous membranes of the tongue, throat, soft palate, and esophagus thickened in increasing degree to the cardia, with a crumbly, dry, yellowish white layer. The lung apices were thick with caseous nodules and cavities. A few small caseous mesenteric glands. Liver capsule thickened. A group of enlarged glands near the aorta.

Microscopical Examination.—Organisms in the ventricular fluid, but none in the brain substance, or in the ependyma or choroid plexus. Large numbers of these in the meninges, a few within cells, but with no reaction of tissues, except occasional collections of lymphocytes. No organisms were seen in the vessels or vessel walls. The esophagus showed loss of epithelium, with a fibrinous deposit; joined organisms penetrated even to the striated muscle beneath. No mycelium was found. Cultures from the throat gave organisms similar to those from the meninges, with no mycelium formation.

Organisms.—The organisms in the lumbar puncture were found to be elliptical or ovoid, and equal in size to a red blood cell or slightly smaller. They almost always had typical yeast joinings to the number of two to four elements. The long diameter varied from 3.33 to 8.33μ, the width from 2.2 to 6.66μ. The small ones were usually ovoid; the large ones approached a spherical form, and often had a double contour. One or two poorly marked eccentric oval nuclei were present, and one to eight refractive droplets. Many giant forms of from 10 to 15μ were found, which were more refractive, with larger oil droplets, a double contour, frequent yeast joinings, and a Gram-negative capsule. The phagocytized cells showed a clear capsule almost equal in width to the yeast cell.

Cultures.—Mycelium formation was never found. The yeast grew least well on bouillon, gelatin, and agar. Growth appeared in 4 to 5 days and then proceeded slowly. No liquefaction of the gelatin took place. Glucose was not fermented. The best growth was obtained on glucose-agar. No spore production was noted.

The atrium of infection was considered to be the throat.

Case 3.—Reported by Eisendrath and Ormsby. Final report by Le Count and Myers.

Patient.—A Polish laborer, 33 years old.

Illness.—Discomfort in the right chest for 6 months, then numerous cutaneous lesions, followed in 4 months by edema of the face and extremities, muscular weakness, emaciation, pallor, and elevated temperature. Shortly before death incontinence of urine and feces was frequent. Death occurred during a convulsion, after 30 months' illness.

Autopsy.—Blastomycotic bronchopneumonia; blastomycosis of the peribronchial lymph nodes, of the pleura, the subpleural and retropharyngeal tissue, the liver, kidneys, colon, spinal column, external spinal dura, cerebellum, left elbow, both knee and ankle joints, skin, and subcutaneous tissues. Emaciation.

Cerebellum.—On horizontal section nearly the entire external half of the right lobe was involved in coalescent areas of softening with wide margins of necrotic tissue in which small nodules were present.

Microscopical Examination.—Small areas of necrosis surrounded by granulation tissue and inflamed cerebellar tissue. The margins of the lesion were made irregular by very minute abscesses, some no larger than a fat cell, containing mono- and polymorphonuclear leukocytes and organisms multiplying by budding. Giant cells containing organisms were found at the periphery of the larger lesions. The granulation tissue often occurred in peculiar masses, containing many cells of chronic inflammation, and very small non-budding blastomycetes. Several large empty capsules were found, with numerous small forms near by. Intact large forms contained several granules resembling nucleoli, with pale areas occasionally visible about them. The small forms each contained one granule. These appearances to the author indicated endosporulation.

Cultures.—Cultures from the cutaneous lesions and the sputum gave spherical and oval organisms, much fine and coarse mycelium, later conidia and aerial hyphæ. Guinea pigs inoculated with the material developed local lesions.

Case 4.—Reported by Krost, Stober, and Moes.

Patient.—A Pole, 42 years old, resident in the United States for 4 years.

Illness.—Pulmonary symptoms, then skin lesions. No brain symptoms were noted except moroseness and irritability toward the end. Blood cultures positive for blastomycetes. Duration of illness, 6 months.

Autopsy.—Miliary and nodular blastomycosis of the lungs, kidneys, spleen, cerebrum, pleura, and lymph nodes. Multiple blastomycotic abscesses of the cerebrum, cerebellum, prostate, pleura, skin, and osseous, muscular, and cutaneous tissue. Parenchymatous nephritis. Fatty changes, adenoma, and angioma of the liver. General lymphatic hyperplasia. Atrophy of the testicles.

Brain.—Weight 1,400 gm. No gross lesions externally. On section, an abscess 2 mm. in diameter was found in the cortex near the middle of the parieto-occipital sulcus. A small nodule was found in the right parietal lobe, one in the right temporal lobe, and two in the occipital lobe; the nodules were in the cortex, usually at the margin of the white matter. There was a nodule in each lobe of the cerebellum.

Microscopical Examination.—There was much necrosis. "Apparent bands of fibrous tissue between adjacent lesions, due to pressure," and numerous "bizarre" giant cells. Blastomycetes were present in the lesions.

Case 5.—Reported by Lewison and Jackson.

Patient.—An Italian, 17 years old, resident in the United States for 4 years.

Illness.—1 year's duration. No nervous symptoms noted.

Autopsy.—Indurated blastomycotic bronchopneumonia of the left lung, blastomycosis of the bones, subcutaneous tissues, pons varolii, inguinal and axillary lymph nodes; acute vegetative mitral endocarditis, fatty liver, parenchymatous degeneration of the kidneys, hyperplasia of the lymphoid tissue of the ileum, edema of the lungs, hydropericardium, atrophy of the heart, pancreas, and testes, emaciation, and anemia. There was one blastomycotic nodule in the brain, a few mm. below the ventral surface of the pons, containing numerous organisms, and apparently formed by the coalescence of small lesions.

No note as to histology.

Case 6.—Reported by Myers and Stober.

Patient.—American.

Illness.—The only symptoms referable to brain lesions were irritability toward the end, with occasional refusal of food and medicine, and delirium a few days before death.

Autopsy.—"Healing and discharging blastomycotic abscesses and ulcers of the skin; blastomycotic abscesses of the bones and muscles; blastomycosis of the lungs, peribronchial lymph nodes, liver, spleen, pancreas, kidneys, cerebrum, and cerebellum; serofibrinous and fibrous pleuritis; parenchymatous nephritis; chronic splenitis; hyperplasia of the mesenteric lymph nodes, pigmentation of Peyer's patches; decubital ulcers; emaciation." The brain lesions consisted of abscesses, about some of which connective tissue walls were present.

Case 7.—Reported by Bechtel and Le Count.

Patient.—A Swede, 38 years old.

Illness.—8 months' duration. No nervous symptoms noted.

Autopsy.—Ulcerative blastomycosis of the upper lobe of the left lung; disseminated blastomycosis of the lungs, liver, spleen, kidneys, adrenals, brain, subcutaneous tissues, and skin; blastomycotic caries of the left iliac and right parietal bones; fibrinous and fibrous pleurisy; hyperplasia of the tracheobronchial, cervical, and mesenteric lymph nodes; red marrow in the femur; emaciation; atrophy of the liver; fibrous mural endocarditis.

Brain.—Fourteen small lesions in the cerebrum, most of them located at the bottom of sulci or at the junction of gray and white matter, a few in the basal ganglia and deeper parts, varying from 2 to 4 mm. in diameter. Two larger lesions in the cerebellum, one 15 by 11 mm. in the white substance between the dentate nuclei and slightly above them, and one 4 mm. posteriorly.

Microscopical Examination.—The histological note states only that there was but little tissue reaction about the lesions.

Case 8.—Reported by Riley and Le Count.

Patient.—An Italian laborer, 31 years old.

Illness.—After an illness of 7 months the first nervous symptoms were noted a few days before death as neck rigidity, slight strabismus, exaggerated reflexes, and a positive Babinski.

Autopsy.—Chronic blastomycosis of the upper lobe of the left lung; erosion of the third and fourth thoracic vertebræ; blastomycotic abscesses of the root of the right lung; disseminated miliary blastomycosis of the spleen and liver; blastomycotic basilar meningitis; abscess of the prostate, peritonsillar tissue, epididymis, and skin (with ulcers), and subcutaneous tissues; caries of the foot bones; multiple intercostal subpleural abscesses; blastomycotic tracheobronchial lymphadenitis; fibrinous and fibrous pleuritis; fibrous peritonitis; emaciation and anemia; brown atrophy of the heart; atrophy of the liver; slight sclerosis of the aorta and coronaries; emphysema of the lungs; ossification of the thyroid cartilage.

Brain.—A thick gray pus or fibrinopurulent exudate covered the base of the brain, thickest over the circle of Willis. Aggregated masses of small size were found in the fundi of the sulci, especially on the right, at times forming marble-sized lesions. No deep lesions were found.

No note as to histology.

Cultures.—Cultures from the cerebrospinal fluid gave a pure growth of blastomycetes.

Organisms in the last five cases were all described in a common cultural report, a partial summary of which follows. In the tissues, discharges, and pus they appeared in pairs or clumps as round or oval bodies, with frequent budding. The size varied from 3 to 30μ, with 20μ as the average size. There was an outer refractile capsule and a clear central portion, the capsule varying in thickness with the size of the organism, and occasionally being invisible in the organisms in old foci. The capsule rarely stained. The central portion was granular and took basic stains, and often contained three to ten spherical basophilic granules. No hyphæ were found in the tissues, and endosporulation was suggested only in Case 3. In cultures there was first a proliferation by budding, then hypha production, and finally a formation of aerial hyphæ. Occasionally segmentation of the mycelium into spores was seen. Another slightly different type had a very fine mycelium and small spores.

Case 9.—Reported by Rusk.

Past History.—Obscure. Previous history of "rheumatism."

Examination.—A confused and talkative patient, becoming exhausted, semi-stuporous, and unintelligent. Pupils irregular and reactive; knee jerks, Achilles jerks, and abdominal reflex absent; diminished pharyngeal reflex; muscular weakness; general diminished sensibility to touch and pain with preservation of temperature sense; some tenderness on pressure over nerve trunks; fine tremor of tongue, coarse tremor of extremities. Temperature 98°F., pulse 108, respiration 26. Stupor.

Course.—Stupor increased, and after an attack of hematuria the patient died. Duration of observed course about 30 days.

Diagnosis.—Senile dementia.

Autopsy. Brain.—Cerebrospinal fluid not cloudy. Frontal convolutions moderately atrophied. The pia was diffusely hazy.

Microscopical Examination.—A chronic inflammatory reaction in the meninges, over the base, along the Sylvian fissure, over the cerebellum and spinal cord, with infiltration of lymphoid, plasma, and large endothelial cells. Giant cells with peripheral nuclei and a circumscribed border were found. Organisms were frequently enclosed in giant cells or endothelioid cells. There were no areas of caseation and no miliary abscesses. The neuroglia of the first layer of the cortex showed a diffuse and general hyperplasia, with increased fibrils and cells. No alterations were found in the nerve cells. In the cortex were two kinds of lesions: first, extensions from the pial lesions; second, circumscribed areas in the basal ganglia, about 1 cm. in diameter, in which the tissue appeared forced apart and filled with gelatinous material. There was a scanty reaction about these lesions of the same type as in the pia.

Lungs.—The left lung contained a group of cavities from the limits of visibility to 2 cm. in diameter, filled with a sticky gelatinous material. Laterally from them was a firm triangular area containing tiny pale yellow foci. Sections from the gelatinous masses showed them to be composed of a spherical, doubly contoured organism, with a sticky, jelly-like capsule of varying thickness, lying in an amorphous matrix. The organism proliferated by budding. The walls of the cavities were formed by fibrous tissue, apparently not newly formed, but the remnant of bronchi or alveoli, which the organisms appeared to be in the process of eroding; the lining cells were swollen, the protoplasm was finely vacuolated, and the nuclei were pyknotic. Some little distance further in the tissue the first evidence of inflammatory reaction occurred, consisting of a slight accumulation of lymphoid and plasma cells, with a few multinucleated cells.

Sections from the firm tissue showed a diffuse chronic granulomatous process with large giant cells containing the organisms. No caseation or interstitial abscess formation was present. Organisms were scattered in the tissue, in cells, and free. Occasional small hemorrhages were present.

No lesions were found in other organs.

Organisms.—Organisms were present in the pia in giant cells, or free singly, or in zoogleal masses. Spherical organisms with a gelatinous capsule, proliferating by budding, filled the lung cavities and were seen in giant cells in the granulation tissue. No cultures were made.

Case 10.—Reported by Rusk.

Patient.—German, 57 years old.

Past History.—Positive for lues.

Illness.—Weakness, morning expectoration, painful muscles, and shortness of breath, were followed by transitory hemiplegias and syncopal attacks, and a temporary loss of speech. Later there were times of confusion and forgetfulness of decencies of dress.

Examination.—Frontal headache and abdominal pain were the complaints. The man was depressed, agitated, perplexed, unable to concentrate his attention, disoriented for time, place, and person; had impaired memory, lack of interest, unstable emotions, poor enunciation with slurring and transpositions; he realized that he was sick, and had no delusions or grandiose ideas. His pupils failed to react to light, the knee and Achilles jerks were absent, the pharyngeal reflex was active. There were ataxia, a positive Romberg sign, a coarse tremor of the face and tongue, diminution in the acuteness of pain and touch over the entire surface of the body with differentiation of temperature. Temperature 101.8°F., pulse 95, respiration 21.

Spinal Fluid.—Positive Noguchi reaction; marked lymphocytosis.

Course.—Increased weakness; urinary retention; death after 24 hours' stupor. Total illness 2 years' duration; nervous symptoms for 10 months.

Clinical Diagnosis.—General paresis, tabetic type.

Autopsy.—Pial haziness and adhesions; cloudy cerebrospinal fluid in the lower part of the spinal canal; a few granulations in the fourth ventricle.

Brain.—Slightly atrophic; weight 1,226 gm.

Microscopical Examination.—The reaction was of the same type as in the previous case with the addition of a few poorly defined miliary abscesses and rare areas with necrotic caseated centers. The meningitis was distributed over the whole cortex. A few small arteries had a subintimal infiltration. Giant cells of enormous size were noted. Organisms were found throughout the pia. There were similar extensions into the cortex, and the same glial reaction. The lungs showed a bronchopneumonia with occasional small bronchi containing parasites, and small granulomatous masses growing from the alveolar walls contained the organisms. Larger granulomatous masses had typical giant cells with the organisms. There was no caseation. Granulomatous lesions containing the organisms were found in the kidney. No cultures were obtained.

Organisms of the last two cases were spherical, doubly contoured, varying in size up to 20μ, with a homogeneous viscid capsule outside the wall, embedded in a homogeneous matrix; staining weakly, with no differentiation of internal structures; the capsule stained with hematoxylin; reproduction was by budding only. Naked forms were seen, free and within cells. Star-like forms occurred after Zenker mordanting.

B. Discussion of Cases.

a. Characteristics of Six Cases Similar to Those of the Usual Form of Systemic Blastomycosis and Cutaneous Blastomycosis.

All but four of these cases had either skin or subcutaneous tissue lesions and presented the usual picture of blastomycotic infection, clinically and in regard to the pathology and the characteristics of organisms in tissues and cultures. The brain involvement was part of a general infection, and clinically, at least, an unimportant part, for no symptoms were produced except in two cases shortly before death,—in Case 3, where the patient died during a convulsion, and in Case 8, in which signs of meningitis were manifested in the last days. We have studied the original reports of all other reported cases of systemic blastomycosis, and have found that in all these there is involvement of the skin or subcutaneous tissues. Stober states that the most characteristic changes in systemic blastomycosis are cutaneous ulcerations, deep and superficial abscesses, and tubercle-like nodules in the viscera. In only three cases has the systemic involvement been the evident result of a spread from cutaneous lesions; in many cases infection in the bronchi and lungs constituted the primary focus, from which dissemination of organisms in the blood resulted in the skin and subcutaneous lesions. Thus a predilection is clear for the development of the blastomycetes in skin and subcutaneous tissues.

b. Four Cases Distinct Clinically, Pathologically, and Bacteriologically.

The four cases without skin or subcutaneous tissue lesions all have brain lesions of such a nature as to cause the predominating clinical symptoms throughout the disease. In von Hansemann's case (Case 1) there were choked disc, slow pulse, unequal pupils, vertical nystagmus, double abducens paralysis, and death following vomiting, involuntary discharge of urine and feces, delirium, and coma. In Türck's case there were headache and frequent vomiting, stiffness of the neck, sensory hyperesthesia, and a positive Kernig sign, the symptoms continuing for nearly 2 months. Rusk's first case had confusion, semistupor, irregular pupils, absent knee jerks, and tremors with death during stupor, 30 days after the first observation. His second case had headache, depression, perplexity, impaired memory, transient hemiplegias, speech disturbance, Argyll Robertson pupils, absent knee and ankle jerks, ataxia, a positive Romberg, and coarse tremor. The diagnoses were as follows: Case 1, tubercular meningitis; Case 2, tubercular meningitis—ruled out later on account of the long duration; Case 9, senile dementia; Case 10, general paresis, tabetic type.

The marked difference in the character of the clinical histories of this group of cases suggests a careful study of the pathological findings in comparison with those of cases of blastomycosis showing skin or subcutaneous tissue lesions. In Case 1 we find the brain lesions consisting of cysts composed of enormous collections of yeast-like bodies embedded in a gelatinous matrix, with very little reaction about them. Numerous large phagocytic cells were in many colonies. In the meninges was an increase in lymphocytes and leukocytes. In the second case the brain lesions showed edema of the meninges, with large numbers of yeast-like bodies, a few of them within cells, with little reaction of the tissues except occasional collections of lymphocytes; the organisms in cells having a clear space about them equal to their diameter; in Cases 9 and 10 there were lesions in the brain consisting of enormous numbers of yeast-like cells with gelatinous capsules, embedded in a homogeneous matrix, with little or no reaction about them; naked forms occurred also; the meninges had a chronic inflammatory reaction with lymphoid, plasma, large endothelioid cells, and giant cells. There was an increase in glia cells. In the second case there were similar lesions but so extensive as to result in areas of caseation. We have had an opportunity to see a section of a brain lesion from one of these cases, and were struck by the fact that the organisms did not produce the lesion by the pressure of their growth, but evidently by a solution of the brain tissue in their immediate neighborhood.

These pictures have no resemblance to those of the brain lesions of blastomycosis with skin lesions. Case 3 showed small areas of necrosis surrounded by granulation tissue and inflamed cerebellar tissue, with minute abscesses in the margins containing polynuclear and mononuclear leukocytes; Case 6, abscesses in the cerebellum and cerebrum, with connective tissue walls; Case 8, a thick purulent exudate over the base of the brain. In the other cases histological notes are very scanty and the assumption seems to be made that the lesions were much like those elsewhere; that is, with acute exudate and granulation tissue. Occasionally the reaction is slight in amount.

Thus the first group of cases is peculiar pathologically (1) in that in lesions within the brain substance there is produced a gelatinous or homogeneous substance in which the organisms are embedded, and about which there is a very slight chronic reaction; and (2) in that there are meningeal reactions of varying degrees of severity, but always containing only cells of chronic inflammatory type. In the cases of blastomycosis with skin or subcutaneous lesions, the brain lesions are described as abscesses with varying amounts of granulation tissue about them, or in one case as a purulent meningitis.

It is important to know whether lesions in other organs differed also. In Case 1 there were lesions of tuberculosis in the lungs, but no other lesions. Case 2 had a lesion in the esophagus with the same organisms as in the brain lesions, and caseous nodules and cavities in the lungs (due to tuberculosis?). There were no other lesions. Case 9 showed lesions in the lungs similar to those in the brain, with sticky gelatinous material and only a very slight chronic reaction; also areas of a chronic, non-caseating granulomatous process with large giant cells. Case 10 had a bronchopneumonia, and granulomatous lesions in the lungs and kidney like those in the previous case

Granulomatous lesions occur in ordinary blastomycosis, but the lung lesion in Case 9 is distinct. The freedom from extensive lesions in other organs in comparison with the usual cases of systemic blastomycosis, and the limited distribution of the lesions, are striking.

In the special group of cases the organisms produced the gelatinous material in three instances; in the second case there were no lesions in the brain, but wide clear zones occurred about the organisms when in cells. The organisms in Case 1 were not described fully; in Case 2 they were elliptical or ovoid, from 3.33 to 8.33μ in length, from 2.2 to 6.66μ in width, the large ones more nearly spherical, with a double contour. The interior contained only one or two eccentric oval masses and a few refractive droplets. Giant forms from 11 to 15μ were found. In Cases 9 and 10 the organisms were placed in a homogeneous matrix and had wide clear spaces or gelatinous capsules about them, varied in size up to 20μ, and had little or no differentiation of internal structure. In every case multiplication was by budding. No mycelium could be found in any of the cases, in tissue or in culture. In Cases 9 and 10 radiating projections from the cell wall were noted after certain stains. The walls of these organisms stained easily. These descriptions are markedly different from those of the other group of cases, in which the organism appears in tissue as a sphere from 10 to 15μ in diameter, with little or no space between it and other cells, but with a space between the cell wall and the central protoplasmic mass, which is finely granular and stains well, as a rule. The cell wall has poor staining qualities. No notes of gelatinous material in the brain lesions ever occur.

Cultures from the first case did not grow; from the second case cultures yielded organisms which did not produce mycelium or endospores even after long observations; from the ninth and tenth cases cultures were not obtained. Cultures of blastomycotic organisms sooner or later produce mycelium.

This group of cases then is distinct clinically, and pathologically from the cases of blastomycosis producing skin or subcutaneous tissue lesions.

In a search for other cases to be correlated with these we found the case described by Frothingham, through whose kindness we have seen sections and have procured tissues and cultures. Part of a lobe of the right lung of a horse was enlarged, pinkish yellow, and gelatinous, microscopically showing a loose connective tissue network with budding organisms embedded in a homogeneous gelatinous matrix. The other organs of the horse were not examined. The organisms had for the most part a homogeneous non-granular interior, containing only a few fat droplets. The cellular reaction included varying numbers of large mononuclear cells, numerous giant cells, and some connective tissue. Pure cultures were obtained. They grew in 5 to 7 days, produced a slight amount of gelatinous material, multiplied only by budding, did not produce mycelium, or ferment dextrose, lactose, or saccharose, and did not form spores, even after observations of growth for 12 weeks on gypsum blocks at varying temperatures. They often formed large resting cells, and were facultative anaerobic. After subcutaneous inoculation they produced subcutaneous tissue lesions of the same type as those from which they were obtained. Thus this organism, which was thoroughly studied, was proved to be a torula, distinct from the oidium-like organisms of blastomycosis, and distinguished from true yeasts by the absence of spore production under special conditions.

The organisms found by Tokishige in lymphangitis epizootica of horses produced mycelium in culture; the disease resembled glanders, involving the skin, lymphatics, and respiratory mucous membranes. It has no relation to the case described by Frothingham.

The similarity of the sections of Frothingham's case to the group of cases described above was so great that a series of inoculations of pure cultures of the torula organism into animals was made in an attempt to produce brain lesions for comparison with those of the cases. The results will be given in detail later, but it may be stated here that lesions identical with the brain lesions of Cases 1, 2, 9, and 10 were produced in rats, thus adding to the evidence that these are true cases of torula infection.

4. Cases of Systemic Blastomycosis without Brain Lesions.

The study of the other cases of systemic blastomycosis without brain lesions led us to the conclusion that Buschke's cases of the true yeast infections formed a group distinct from either of the two just discussed. It is a small group; in fact only two undoubted cases can be found. Many cases reported as such, especially in dermatological literature, are incompletely reported, and of doubtful nature, as Buschke himself states. The case of Busse and Buschke was so carefully observed by both, and the pathogenicity of the organism proved so conclusively by inoculations of a pure culture of the organism on the patient's skin, with the reproduction of the lesions, which contained a pure culture, that it can hardly be doubted. The lesions were in the subcutaneous and cutaneous tissues, tibia, left ulna, and left sixth rib, with perirenal abscesses, and lesions in the lungs, kidneys, and spleen. The organism had produced a purulent infiltration in the bones as in streptococcus lesions; in the skin there was overgrowth and destruction of epithelium with many giant cells. The lung contained abscesses bordered by fibrous tissue containing nodular accumulations of small round cells, in which were parasites. The parasites here were not often intracellular. In the kidney was an abscess with acute interstitial inflammation. The whole picture to Busse was that of a chronic pyemia. The organism often had an adventitious capsule in tissues; in culture it fermented sugar and did not produce mycelium, even after long observation under varying conditions; it produced spores readily on gypsum blocks. The reproduction was by budding, with frequent formation of joined bands. In rabbits intraperitoneal injections produced a fresh fibrinous peritonitis, with peritoneal nodules. In some tissues the organism had an adventitious capsule. In mice and rats brain lesions were produced, but no capsule formation occurred. The pathological processes in general were those of degeneration and necrosis, with inflammatory reaction, which varied with the virulence of the culture.

The organism in this case is in a way a transition from the oidium type to the torula. It resembles the oidium type in that the principal lesions it causes are cutaneous or subcutaneous, with internal lesions in the bones, lungs, kidneys, and spleen. It has less attractive power for polynuclear leukocytes, sometimes has an adventitious capsule, and is known to produce brain lesions in animals, in these respects showing a resemblance to the torula group. It differs from the torula group in not having a predilection for the nervous system in man, but in affecting especially the skin, and does not produce the gelatinous matrix. Of course it is distinct culturally in its spore production.

The case of Hudelo, Duval, and Laederich, in which there were subcutaneous and cutaneous lesions, was exactly similar to Busse's, as regards all the characteristics of the lesions and parasites, as Buschke, who studied both, states.

In Curtis' case, where there were multiple subcutaneous tumors of a myxomatous appearance, with little proliferation of connective tissue, and some acute reaction, the organism usually did not occur in cells, measured 2 to 7μ in diameter, and had a clear capsule, with thin layers. In animals it grew in masses with an adventitious capsule, producing little reaction. No mention is made of the presence or absence of sporulation. Fermentation occurred. This case is anomalous. It does not exactly resemble either of the above groups; on the whole, it seems better to leave it unclassified until more observations are collected.

We defer a summary of the differential points of these three groups of true yeast, torula, and oidium infection, into which cases of systemic blastomycosis fall, until the cases to be presented in the paper have added further details.

In the remainder of the paper oidiomycosis will be used to designate the group of cutaneous and systemic diseases produced by organisms budding in tissue and producing mycelium in culture, especially noted near Chicago. The term blastomycosis confuses relationships and should be discarded.

III. TWO CASES OF TORULA INFECTION, WITH AUTOPSIES.

1. *Case I.*

A woman, aged 42 years, a native of Vermont, resident in Florida, entered the Surgical Service of the Peter Bent Brigham Hospital on Aug. 14, 1914, on account of headaches, failing vision, and dizziness of 3 months' duration, nausea and vomiting, diplopia, unsteady gait, difficulty in finding words, and disorientation.

Family History.—No record of definite nervous diseases, or of other significant troubles was obtained. Married for 18 years, with no children or miscarriages.

Past History.—Only minor illnesses. Always troubled with nervous headaches accompanied by lacrimation. Several attacks of sore throat. Mild photophobia habitual. No history of cardiorespiratory, gastro-intestinal, genito-urinary, or skin diseases.

Present Illness.—About May 15 the patient began to have a severe headache, persistent and throbbing, at first frontal, but later occipital, accompanied for the first 2 weeks by a temperature ranging between 98° and 102°F. The headache did not stop; its most recent situation was in the back of the head and neck. Vomiting not preceded by nausea and not related to meals occurred twice, once 2 months before entrance and once a week before. After May 15 the patient's eyes ached and tired easily. Her vision, previously good, deteriorated until only the coarser type in a newspaper could be made out. Diplopia was definite in the 2 weeks before entrance. Dizziness and a staggering gait were present from the beginning of the illness. It was noticed early that the patient at times dropped words and found expression difficult. Faulty spelling and omissions occurred in her letters. Mental dulness began a month before admission, and 10 days before there was said to be complete disorientation for time, place, and person.

Previous Examination.—A choked disc; greater knee jerk on the right; negative Wassermann blood test; white count of 10,200; differential count of polymorphonuclears 58 per cent; small mononuclears 20 per cent; large mononuclears 12 per cent; eosinophils 10 per cent.

On entrance the following data were obtained. The patient was a fairly developed, rather poorly nourished woman, lying with closed eyes, tossing about restlessly, frequently throwing her hands up to the back of her neck and crying with pain in her neck, arms, and shoulders. She was dull, muttered unintelligible words, was completely disoriented for time and place, but apparently recognized her family.

Physical Examination.—Negative except for a blowing systolic murmur, loudest over the 2nd l.i.s., and also heard at the apex, and a white sticky pharyngeal exudate and a heavily coated tongue.

Cranial Nerve Examination.—A symmetrical head with marked suboccipital tenderness. Pressure over the neck and shoulders caused pain. Nerve I: the patient apparently did not recognize coffee. Nerve II: fundus o.u. disc distinctly obliterated; lamina cribrosa gone. Swelling of the cup estimated at 3 to 4 D. Partial and in places complete embedding of the large and tortuous veins. No definite perivascular streaking. Arteries partially embedded. Macular region and peripheral fundus clear. Nerves III, IV, and VI: pupils vary in equality; both react to light; a tendency to exophthalmus. No ptosis. Apparently a slight weakness of the left external rectus. No definite nystagmus. Nerve V: negative. Nerve VII: question of some weakness of the right side of the face. Nerve VIII: slightly better hearing on the right. Nerve IX: definite dysarthria. Nerve X: pulse regular, very slight vomiting. Nerves XI and XII: negative.

Cerebrum.—Frontal: memory—some past memory; practically no recent memory. The patient knew where she was born and schooled, but did not know whether she had had breakfast or not. Orientation: completely disoriented for time and place, but not for person. Habits and disposition: marked change. The patient had become very disagreeable. Phases of negativism brought out during the examination were evidenced by poor cooperation, refusal of orders, etc. Temporal: a suggestive but not definite history of aphasia. None made out on examination, although a certain amount of dysarthria was present. No uncinate gyrus attacks or dreamy states. No hemianopsia on rough test. Parietal: negative for sensory and motor disturbances. Occipital: negative.

Cerebellum.—Romberg positive with eyes open, the patient tending to fall backward and more toward the left, even on a wide base. Gait: very uncertain, although the patient was able to walk, with staggering, especially to the left. Ataxia: negative. Tests: finger to nose test fairly well performed, right and left. Heel to knee test not cooperated in. Vertigo: some on standing. Diadokokinesia: fairly well performed.

Reflexes.—Superficial: epigastric, abdominal, and plantar not elicited. Deep: no biceps, triceps, patellar, tendo Achilles, ankle clonus, Babinski, Gordon, or Oppenheim on either side. Sphincters: not disturbed.

Positive Findings.—Objective: patient dull, muttering, disoriented for time and place, complaining of pain in the neck, arms, and shoulders; with suboccipital tenderness, questionable anosmia, marked choked disc, occasional inequality of pupils, possible weakness of left abducens, marked dysarthria, impaired memory, changed disposition and habits, positive Romberg, deviation in gait to the left, with uncertainty; and no obtainable superficial and deep reflexes, Kernig negative. Tongue and pharynx heavily coated.

Course of the Case.—On Aug. 15 a considerable resistance to flexion of the neck was noted. The left side of the face apparently moved less well than the right. There seemed to be great pain in the back and neck. No definite Kernig was found. Suboccipital tenderness and some fine nystagmiform twitches were discovered, but there was no outspoken nystagmus.

There was no marked extracranial dilatation of vessels, and no visible lack of parallelism of globes, although diplopia was complained of. The mental disturbances with rambling speech were striking features. The diagnosis was thought to depend upon internal hydrocephalus or general pressure.

Operation.—On Aug. 15 a right subtemporal decompression was done. The dura showed no abnormality other than increased tension. On incising the dura the brain appeared tense, and exuded fluid freely. There was some excess of fluid in the subdural and subarachnoid spaces. No fluid was obtained on attempted ventricular puncture.

Aug. 18. X-ray examination of the head was negative. Eye examination showed a disc elevation of 1½ to 2 D with considerable perivascular streaking about the disc. Venous engorgement and tortuosity were still present to a moderate degree, and a few fine punctate hemorrhages in both discs, with partial embedding about the disc.

On Aug. 20 the left pupil was considerably wider than the right. On Aug. 21 Cheyne-Stokes respiration set in. The decompression wound was bulging and tense. There was marked carphology. The face was puffed more to the left, and the left lower side seemed weak. The head was constantly turned to the left, and the right leg was moved much more often than the left. The plantar reflex alone could be obtained. The temperature was 103°F.

On Aug. 27 examination of the chest showed dulness to percussion over the lower half of the left back with high pitched tubular breathing and many fine crackling râles. At the extreme base the note was flat and the signs were distant. A diagnosis of lobar pneumonia was made, with beginning pleurisy with effusion.

After a period of profound stupor, the patient began to respond imperfectly to questions. The left facial paralysis became more marked. The optic nerve head was 1½ to 2 D higher, and little punctate hemorrhages were visible in the left eye. The head was still held to the left and resisted straightening. The left pupil was still dilated. The arm and leg on the right were never used spontaneously, but the right arm was drawn back on pin prick. The right knee jerk was elicited for the first time. The hands moved aimlessly. There was a normal plantar reflex on the right.

The patient became rapidly worse, with cyanosis and dyspnea, and died on Aug. 27, at 7.30 p.m.

Clinical Pathology.—Urine examination: specific gravity 1,011 to 1,022; albumin, trace. Sugar 0. Sediment: bacteria, squamous cells, a few white cells, very rare granular casts.

Blood examination: white count, on Aug. 14, 11,000; Aug. 17, 16,200; Aug. 20, 34,300; Aug. 26, 25,200. Hemoglobin 90 per cent (Talquist).

Temperature course (rectal) on entrance 99.5°; on Aug. 15, 101.5°; on Aug. 17, 103.8°; then variations from 101.8° to 103.8° until 2 days before death when it was 102°.

Autopsy.—Permission for a complete autopsy was obtained and the examination made on Aug. 28, 13 hours post mortem. The body was put in a refrigerator immediately after death. The brain was hardened *in situ* by an injection with 10 per cent formalin through both carotid arteries.

Body.—The body is that of a slightly built, normally proportioned white woman, 165 cm. long. The skin is smooth, white, and free from edema or pigmentation. There are no discharges from external orifices, and no palpable glands. There is slight postmortem rigidity and lividity. The head shows a slightly bulging area, the site of a right subtemporal decompression operation. The pupils are equal and measure 4 mm. The chest is narrow and small. The breasts are slightly developed. The abdomen is level. The extremities show no abnormalities.

Primary Incision.—There is found to be a thin layer of abdominal fat and thin musculature.

Peritoneal Cavity.—The omentum is free from adhesions and contains a small amount of fat. There are about 20 cc. of clear, very slightly blood-tinged fluid in the pelvic cavity. The peritoneal surfaces are smooth, gray, and glistening, and there are no adhesions. The mesenteric and retroperitoneal lymph nodes are of normal size. The gastro-intestinal tract appears normal. The liver extends 4 cm. below the xyphoid and 3 cm. below the costal margin in the right mammary line. The diaphragm ascends to the fifth space on the right and the fourth space on the left.

Pericardial Cavity.—The pericardial sac contains about 10 cc. of clear yellow fluid; the surfaces are smooth and the heart lies entirely free within the cavity.

Heart.—Tricuspid valve 10.5 cm.; pulmonary valve 6.5 cm.; mitral valve 9 cm.; aortic valve 5.8 cm. Right ventricle 3 mm. thick; left ventricle 12.5 mm. thick. Weight 250 gm. The foramen ovale is closed. The endocardium covering the cavities is normal. Except for slight diffuse thickening of the edges of the tricuspid valve and slightly more focal thickening of the edges of the mitral valve with slight roughening of the endocardium, the valves appear normal. The aorta shows a few small plaques of sclerosis, especially about the orifices of the coronary arteries. The coronary arteries are open throughout their extent. The heart muscle is pale and appears slightly yellowish, but is uniform throughout.

Right Lung.—The right lung is crepitant and slightly more firm than normally. The external surface shows a light deposit of carbon, and lividity at the base. The cut surface shows the carbon in a slightly moist, pinkish gray surface with distinct alveoli. At the tip of the apex is an area 0.5 cm. in diameter, apparently composed of fibrous tissue. The middle lobe has a slightly paler and moister external surface, but on section shows a reddish surface with scattered lighter areas apparently connected with the bronchi, exuding a thin white pus on pressure. The lower lobe is similar, but shows in addition slight congestion. The bronchi have a reddened mucosa with much purulent matter. The bronchial lymph nodes do not seem enlarged.

Left Lung.—The upper lobe is similar to the right upper lobe. The lower lobe is dark purple externally, and more solid than any of the other lobes. It is deep red and homogeneous on section. Pieces sink rapidly in water. The bronchi contain little pus, and there are no areas of induration about them. The bronchial lymph nodes are smooth and pale, with black streaks of carbon.

Liver.—Weight 1,205 gm. The external surface appears normal. Section shows greatly dilated and reddened central veins. The gall-bladder and bile ducts appear normal.

Kidneys.—Right weighs 120 gm.; left 145 gm. The right appears small and the capsule strips with some difficulty, leaving a finely granular surface in several places. The tissue cuts with slightly increased resistance. The vessels are congested. The glomeruli are visible. The left kidney is similar to the right except for a larger size, smoother surface, and less adherent capsule.

Spleen.—Weight 125 gm. The external surface is normal. On section it is pale with prominent Malpighian bodies.

Pancreas.—Appears normal.

Adrenals.—The medulla is soft,—almost liquefied.

Gastro-Intestinal Tract.—There is no sign of ulceration or inflammation.

Bladder.—Appears normal.

Genitalia.—The vagina appears normal. The external *os* is extremely small and leads into a small cavity into which the probe point of small enterotome scissors can hardly enter. Just at the level of the internal *os* the uterine wall contains a small nodule 1 cm. in diameter, whiter and harder than the rest of the uterine tissue. The left ovary is almost entirely converted into a sac containing bloody fluid. There is a slight amount of ovarian tissue surrounding the sac. The wall of the cyst has a smooth gray internal surface, and is about 1 mm. thick. The ovary is freely movable. The right ovary has a number of yellowish hard areas; on section one of them is circular, placed near the outer surface, and 4 mm. in diameter. The pelvic peritoneum covering the organs appears normal.

Aorta.—The aorta has a few sclerosed areas in the abdominal portion, especially

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about the orifices of the branches, but they are slight, usually not measuring over 5 mm. in diameter, and little raised above the surrounding intima.

Lymph Nodes.—A calcified mediastinal lymph node is found, but the bronchial, mesenteric, and retroperitoneal nodes are free from signs of tuberculosis.

Head.—On removing the calvarium the dura is found to be free from adhesions to the skull except about the margins of the subtemporal decompression site. The dura is grayish white. The internal surface of the calvarium appears normal. When the dura is stripped back a number of not very strong white adhesions (more than the normal number) passing to the pia are found. The base of the skull appears normal.

Brain.—The brain is of normal size. The pia is definitely thickened, and more adherent than normally. On the right side of the brain in the temporal region, at the site of the decompression, is a hernial protrusion. The vessels and nerves at the base of the brain appear normal; there is no arteriosclerosis. On removing the meninges from the frontal lobes the convolutions appear slightly atrophied, with slight roughening of the surface by the presence of very small pits which are barely visible. There is some flattening of the convolutions over the whole brain. Asymmetry is evident, the right side being broader, especially in the temporal region.

On section the lateral ventricles are found to be dilated, the right more than the left. There seems to be no ependymal thickening, but the choroid plexus appears slightly thickened. The aqueduct of Sylvius is blocked in the posterior two-thirds by dense white tissue.

Serial sections of the whole brain, about 3 to 6 mm. thick, were made in a frontal plane. Frontal lobe: gray matter 3.5 to 5 mm. thick. Meninges in the depths of the sulci much thickened. The following lesions were found. In the left superior frontal gyrus, 2.3 cm. from the anterior tip of the lobe, is an area in the gray matter, bordering on the meninges, 2.5 mm. in diameter, filled with colorless gelatinous matter amid which are fine white dots and threads. Some of the threads are adherent to the edge, others pass across the middle. In the same convolution, 4 mm. further back, are two similar lesions in the gray matter at the border of the white matter; one 0.5 mm., the other 0.25 mm. in diameter, separated by a distance of 0.125 mm. In the same gyrus at the level of the tip of the caudate nucleus are two similar lesions, 0.5 mm. from the upper surface of the gray matter, measuring 0.33 and 0.25 mm. The right superior frontal gyrus contains several similar lesions; one 0.5 mm. in diameter, just anterior to the caudate nucleus, another 0.25 mm. in diameter, 0.25 mm. further off. One at the tip of the caudate nucleus is 3 mm. in diameter. At the level of the anterior tip of the temporal lobes a lesion 0.75 mm. in diameter is found, 0.125 mm. from the upper surface of the cortex, and a similar lesion in the white matter 1 mm. below the gray matter. In the middle frontal gyrus is a lesion 0.75 mm. in diameter.

The right temporal lobe has an area 2 by 1.3 cm., extending mesially 1.5 cm. from the surface, and including the whole middle and part of the superior temporal convolutions, where there is loss of substance and granulation tissue (area of decompression). For 0.9 cm. back from this are minute spots of hemorrhage in the gray and white matter. Back of this decompression area, in the inferior frontal gyrus, just above the insula, is a lesion 1.6 by 1.5 cm., extending 1.6 cm. within the surface, of similar character. The internal capsule of this side is very soft.

Basal Ganglia.—The superior part of the putamen of the lenticular nucleus has many small lesions about 0.5 mm. in diameter, similar to those in the frontal lobe. Several coalesce into a streak 4 mm. long, Y-shaped.

Occipital Lobes.—Similar lesions in the precuneus, 4.8 cm. from the tip of the lobe. One is 1 mm. in diameter, and extends from the gray into the white matter; another is 2 by 1 mm.

Cerebellum.—In the right lobe, on the upper border, is a sharply circumscribed area 4 by 6 mm., of translucent rather mucoid appearance, surrounded by a white zone.

Corpus Callosum.—On the left is an area where the corpus callosum is swollen, softened, and apparently disintegrated. It is 7 mm. in diameter here as compared with 5 mm. on the other side. This is evidently the track of the needle used in the ventricular puncture.

The perivascular spaces throughout the brain appear slightly dilated, and often contain a small amount of gelatinous material.

Symmetry.—At the anterior end of the thalamus the greatest width—measured to the midtemporal convolution—is 7.7 cm. The left side at the same level is 6.1 cm. broad. The white matter on the right side appears much wider. The lateral ventricles have abnormal shapes; the general alteration in angles is apparently due to a combination of dilatation and drawing to the right which is the result of the herniation.

The lesions in the right temporal lobe and the corpus callosum, and the asymmetry, are evidently the result of operative procedures.

Anatomical Diagnoses.—Right subtemporal decompression, right ventricular puncture. Internal hydrocephalus (slight). Occlusion of the aqueduct of Sylvius. Subacute or chronic meningo-encephalitis of unknown origin, with multiple foci of infection in the cerebellum, cerebral cortex, and basal ganglia. Lobar pneumonia of the left lower lobe. Left pleurisy with effusion. Slight bronchopneumonia of the left upper and right middle and lower lobes. Subacute mitral endocarditis. Calcified mediastinal node. Passive congestion of liver and spleen. Slight ascites. Slight chronic interstitial nephritis. Leiomyoma of uterus. Stenosis of cervical canal. Cystic left ovary. Postmortem softening of adrenals.

Microscopical Examination.

In general, a chronic leptomeningitis, consisting of the accumulation of lymphoid, large phagocytic mononuclear, giant, and rarely polymorphonuclear cells, with formation of connective tissue, especially about vessels, and with occasional caseous areas, is found over the cerebrum, cerebellum, and spinal cord. Enormous numbers of spherical organisms, of varying size, with a definite wall, intra- and extracellular, are present everywhere in the lesions. There are areas of necrosis, but no circumscribed tubercles. Foci of infection of two kinds are seen within the brain. One consists of a perivascular lesion resembling the meningeal lesions. The other presents itself as a small, spherical space in the cerebral tissue, filled with a non-staining matter in which are embedded singly large spherical dark staining organisms, which are occasionally seen budding. Few reactive cells are seen within or around the lesion. The only reaction consists of a very slight increase in glia tissue close to the lesion, and a moderate number of large epithelioid cells and lymphocytic cells within the lesion. The cerebellar lesion is of this second type. The more general reactions of the brain consist of a marked cortical gliosis, and a diffuse slight degeneration of ganglion cells and myelin sheaths.

Meningeal Lesions.—The meninges are thickened in varying degree, with connective tissue infiltrated with large phagocytic mononuclear, giant, lymphocytic, and plasma cells. The most extensive lesion is adjacent to the hippocampus; a somewhat less advanced lesion is in a section of the island of Reil. The lesions are more extensive in the sulci; in some regions of the cortex there is but little cell increase.

The advanced lesions show areas of necrosis or caseation, resembling that seen in tuberculosis. In detail, these areas include a caseous center, staining pink with eosin, in which indistinct remains of endothelial and lymphocytic cells, and organisms, can be seen. Often a moderate amount of fibrin, in fine threads, is present in the caseation, but is more apt to be seen at its border. Immediately surrounding the caseous material is a layer of elongated nuclei radially arranged, some of which have fibroglia fibrils along their periphery. Numerous large phagocytic endothelial cells and a few lymphocytes are present in this zone. Beyond is a thin band of connective tissue containing a few giant cells. In other places vessels may be seen surrounded by increased connective tissue, beyond which are caseous zones.

Between the areas of caseation the lesion consists of connective tissue of varying density, but on the whole reticular, in the meshes of which are included many plasma, giant, lymphoid, and large phagocytic mononuclear cells.

This chronic inflammatory tissue has many small spaces, entirely or partially filled with the organisms to be described later. These spaces for the most part are formed by the solution of the protoplasm of endothelioid or giant cells. Often in necrotic material a small space about 10 to 15μ in diameter is seen to contain an organism in the center. Giant cells are numerous and occur in two forms: one with eight to ten centrally located oval nuclei; the other with more spherical nuclei, peripherally located, and often entirely surrounding the central part of the cell. Organisms are at first peripheral in both forms, and occupy only the central portion after the outer portion has been destroyed or filled. The giant cells, as a rule, are not especially associated with nodular thickenings, but they occur diffusely. There are no areas of acute exudate. Polynuclear leukocytes are extremely rare.

Vascular Changes.—The most frequent vascular change in the meninges is a proliferation of the adventitia of the vessels. Sometimes the endothelium is raised by a few mononuclear cells, or is swollen, with a deposit of brownish pigment back of it.

Distribution.—Over the greater part of the cortex the meningitis has not progressed to the point of necrosis or caseation, and corresponds to the lesion just described as occurring between the areas of caseation. Where there is the least amount of meningitis, the meninges show slight thickening, a good deal of edema, and comparatively slight cellular infiltration. A greater or less degree of meningitis is present in all parts of the cortex.

Organisms.—Besides the organisms to be described later no others could be found after search in sections stained with methylene blue and eosin, the tubercle bacillus stain, and the Levaditi stain.

Reaction of the Cortex.—Throughout the cerebral cortex there is great peripheral gliosis, varying somewhat in intensity. This takes the form of a dense cortical felt-work of fibers as much as 28μ thick in the sulci, and 8 to 10μ on the convexity of the convolutions. In the subcortical regions are large numbers of neuroglia spider cells, and some increase in glia cells extends down to the ganglion cell layer. The fibril formation is relatively more marked than the cellular reaction, but the large cells in close relation to fibrils are very evident. In the marginal gliosis no cells are seen.

Organisms in the Meningeal Lesions.—The size varies from 1.25 to 9μ. The large forms are spherical and have a wall 1μ thick; the smaller forms, which occur most often, measure about 3.5μ in diameter, and have a wall about 0.25μ thick; many are ovoid, the diameters being 2.75 by 3.5μ, or 3.75 by 4.25μ. Measurements of some of the smallest forms are 1.5 by 2μ, or 1.25 by 1.5μ; some appear to be 1μ in diameter. The wall is so thin in these very small forms that it cannot be made out definitely.

The organisms are refractive and of a round or oval shape; the larger ones have a wall appearing as a double line with a deeper staining enclosed space; the smaller ones have thinner walls, so that those about 3μ in diameter have a wall appearing as a single line of definite thickness. As stated above it is difficult to make out the presence or absence of a wall in the very smallest forms, but the regularity of shape and the refractility suggest that there is a definite membrane about the protoplasm. Sometimes the organisms stand out prominently; at other times they are difficult to see without special stains. With hematoxylin the inner line of the wall stains as a definite, sharply defined line, slightly thicker than the extremely thin line outlining the outer surface. Cresyl blue gives a similar staining reaction. With both, as well as with methylene blue, the wall stains diffusely, so that the double contoured part appears darker than the central part. Partly degenerated organisms lose their staining properties. Mallory's aniline blue connective tissue stain colors the walls of the organisms a faint blue, and they stand out prominently in contrast to the red tinge of the surrounding tissue. Levaditi's stain colors them a yellowish brown, giving a strong contrast to the light staining tissues. The very small organisms do not show evident coloration of the wall with any staining reagent tried; consequently their presence might easily escape notice; but this absence of coloration makes it easy to distinguish them from nuclear detritus; while their refractility makes a less easy distinction possible from products of degeneration. A stain with iodine results in slight brown coloration of the outer part of the wall of the largest organisms; in the smaller ones no staining can be seen.

Interior of Organisms.—Usually eccentrically placed, is a small particle, about one-sixth the diameter of the organism, roughly spherical, which takes nearly all stains slightly,—cresyl blue, Marchi, methylene blue, and Scharlach R. It is present especially in the smaller organisms. In the largest ones it is almost invariably absent; and it is often absent in organisms of all sizes. In frozen sections stained with cresyl blue the cell interior is best made out,—and then it is found that besides the material just described, there are varying numbers of particles about one-half its size. The masses are sharply outlined, and vary in size and number without relation to the size or budding of the organism. In formalin-fixed material teased out and mounted in glycerine or in salt solution plus a drop of 10 per cent sodium hydroxide, these masses appear more refractive than the organism, but less refractive than fat; they have the same refractility as the droplets usually present in fungi. The organisms do not show a clear zone between the cell wall and the cell protoplasm, as is usual in the organisms of blastomycosis. The study of the cell interior is unsatisfactory in the meningeal lesions on account of the age of the lesions and the degeneration of most of the organisms.

Variations from the Usual Forms.—Occasional organisms are irregular in outline, appearing partially collapsed, or are broken in places, or are open showing a cup-like interior. These broken forms, except in their size, resemble red blood corpuscles. They also differ in often having a jagged or pointed edge, and in having different staining properties.

Reproduction.—The organisms occur in enormous numbers in the meninges, but evidence of a method of reproduction is at first difficult to find; probably because the lesion is a very old one and not progressing. The empty capsules suggested endosporulation, but no evidence of such a process could be found. Budding was more strongly suggested by the frequent occurrence in apposition of a large form and a small form. Many definite buds were found, the protoplasm of the larger cell flowing out, then becoming constricted to form a new cell one-third to one-half the diameter of the original one. In one case a cell 3.75 by 4.25μ was producing a bud 1.5μ in diameter, which was partially separated by constriction. Budding occurred most frequently in the medium sized forms; it was made out definitely, however, in the largest and the smallest forms. The buds have thinner walls than the parent organisms; some have no visible wall.

Occurrence of Organisms.—The greater part of the organisms occurs in giant cells. Sometimes one-half of a giant cell is represented by a space in which are four or five organisms; one arrangement is a space containing one organism about 3 to 4μ in diameter, and three to four organisms 1.5 to 2.5μ in diameter. The organisms lie in the space separated from each other, unless they are budding. In other cases the organisms pack the giant cells full of spherules 3 to 4μ in diameter, the protoplasm and nuclei of the giant cell having entirely disappeared. Sometimes the bodies occur diffusely through the outer portions of the giant cell, with very slight spaces, or no spaces, about them. These organisms usually show no central masses. The organisms are often found in phagocytic mononuclear cells, having the same relation to the cell as in the giant cells. Many organisms occur extracellularly. These usually have a more or less spherical space around them about two to two and a half times their diameter, especially when the organisms are large or when they occur in necrotic material. The spacing of the organisms in necrotic tissue gives a honeycombed appearance.

The larger organisms often have fine threads connecting them, which stain easily with methylene blue. The threads are a little larger near the organisms, taper slightly to a place midway between them, are a little irregular in outline, apparently are attached to the cell wall, and cannot be made out to have a wall themselves. Occasionally they are apparently formed by the separation of budding cells, and on the whole do not appear at all like mycelium. They suggest some mucoid or gelatinous substance which is drawn out into threads as reproduction and separation take place, or is shriveled into filaments by the action of a fixative; in short, they represent some extracellular substance about the organisms. These filaments are more prominent in the intracerebral lesions than in the meninges.

Relation of the Organisms to the Cells.—The phagocytic giant cells show all stages of degeneration. There may be spaces like those just described, probably resulting from a solution of the substance of the cell; the nuclei become pyknotic, the remainder of the protoplasm becomes finely vacuolated and stains faintly; finally the nuclei disappear; then the protoplasm vanishes, and a space which is occupied by a few organisms or packed full of them remains, bordered by the old edge of the cell. When the organisms occur without spaces about them the giant cells do not show such degeneration; it is probable that in this case the giant cell has taken up dead organisms which have not been able to destroy it.

Intracerebral Lesions.—In the cerebral cortex, in the cerebellum, and in the basal ganglia are lesions peculiar in the mode of extension and in the reaction.

The Cerebellar Lesion.—This lesion measures 0.45 cm. in diameter and consists essentially of a solution of the cerebellar cortex and a filling up of the space by a colony of organisms, each separately placed in a gelatinous matrix. Strands of tissue are seen crossing the cavity, consisting of remains of the granular and molecular layers, in apparently good condition. No layer seems to be more susceptible to the destructive influence than another, and the almost spherical outline of the lesion shows that the periphery is being extended uniformly without regard to the tissue. The extension is plainly by solution of the tissue, and not by the pressure of the organized mass. Small masses of organisms, or even individual organisms, can be seen sinking into the molecular or granular layers. Numbers of hyaline remnants of cells, some of which were apparently large phagocytic mononuclear cells, others lymphocytes, float in the cavity, and in one place form a layer at the periphery. The small organisms often pack these cells. No polymorphonuclear, plasma, or red blood cells, no newly formed connective tissue, and no bacteria can be found within the cavity.

Organisms in the Cerebellar Lesion.—The usual size is from 9 to 13μ. Smaller ones 6μ in diameter are frequent; occasional organisms are 3.5μ in diameter. Near the periphery of the lesion organisms 1.5 to 2μ occur rarely.

The organisms are spherical, and thick walled. The wall stains a deep blue with methylene blue. Perhaps on account of the thickness of the cell wall, no differentiation of the cell interior can be made out. The organisms are homogeneous throughout, with a certain clearness quite different from the solidity of corpora amylacea, and the frequent occurrence of broken forms shows them to be hollow spheres with thick walls. Often the outline of the organism is uneven, as if there had been crushing, or partial collapse from the process of dehydration. The smaller forms appear like the organisms in the meninges. Threads connect the organisms as in the meninges, but they are thicker and more definite in this lesion. With a cresyl blue stain it is seen that the lesion is nearly filled with a substance staining faintly which surrounds the organisms. This is irregular in outline, very variable in extent, and resembles a mucoid or gelatinous material which has been formed as a result of the activity of the organisms and has constricted during the processes of preparation, so that it adheres to and surrounds the solid materials in the cavity. The threads seen in the methylene blue stain are thickenings in this material, formed by the drawing apart of the organisms or the shrinkage of the material. With the cresyl blue stain radiating thickenings often project from an organism in great numbers, giving it a star-like appearance. Rusk has described similar forms and they resemble the gelatinous deposit described by Klein, Cohn, Busse, and Nichols in their experiments with torulæ, and seen by us in our experimental lesions in animals. It results in holding the organisms in their peculiar separate placing. Budding forms are rare in this lesion. Sometimes there is an appearance as of successive buds, the budding cell itself budding before it is separated. No appearances at all suggestive of endospore formation are seen. These large forms with thick walls and few evidences of reproduction seem like involution forms or like resting cells. They suggest the large cells found in old cultures of torulæ. The conclusion is evident that the lack of reaction is not to be explained by a postmortem invasion of the organisms; these large thick walled forms with little evidence of activity and the presence of the desquamated mononuclear cells indicate the end-stage of an old process.

Reactions of the Cerebellar Tissue to the Lesion.—On account of the relations of the meninges in the cerebellum it is difficult to say what reaction is due to the meningeal lesion and what to the internal lesion. There is a slight but definite increase in the glia tissue of the cerebellum near the lesion, most marked where the infected meninges are close; and since it is also plainly visible in the strands of molecular layer floating in the lesion, and indeed is more marked here than beyond the periphery, it is probable that there is a slight reaction of the glia to the internal lesion.

Degenerations in the Cerebellum.—On one side of the lesion the Purkinje cells appear slightly shrunken and elongated, the nucleus is poorly marked, the Nissl bodies are not clearly cut, and, toward the periphery of the cell, the cell protoplasm takes an abnormally deep blue with methylene blue and has a somewhat cloudy appearance. This change is more marked near the lesion than at a distance from it; but around a considerable part of the lesion no change is demonstrable.

Other Lesions within the Brain.—Lesions similar to the cerebellar lesion in all respects except size are found in sections of the basal ganglia. There is the same slight invasion with the large phagocytic mononuclear cells, the same slight reaction of the glia cells, the same absence of all acute exudate even in the smallest lesions, the same method of extension by solution of brain tissue with the formation of new lesions, and the same spacing and form of organisms. The differences are that the organisms are, as a rule, smaller than in the cerebellar lesion; the average size is 7 to 8μ instead of 10 to 11μ; the largest is 9μ instead of 13μ; a good many are 4.5 to 5μ, and they occur as small as 2μ. Many of the medium sized or smaller organisms are seen to contain a protoplasm staining dark red, irregularly granular, without definite nucleus. The protoplasm fills the cell. Budding organisms are more frequent here than in the cerebellum.

The cerebral tissue adjacent to the lesion shows little or no change. The pointed projections between the organisms show how these sink individually into the tissue. Often no gliosis can be made out; at other times there is a slight increase in glia cells, more rarely in glia fibrils.

Stages occur from these comparatively non-reactive lesions to perivascular lesions similar to the meningeal lesion. There is more and more cellular infiltration and increase of connective tissue, and less evidence of the peculiar extension by solution of tissue, the organisms becoming more and more intracellular and smaller in size. Often the perivascular spaces become considerably dilated.

Another type of cortical lesion consists of the thrombosis of a vessel with many organisms in the thrombus, with dilatation of the vessel wall, and extension through it, forming a lesion of the first or second type. It is not possible to say whether all the lesions in the cortex arise in this way. It would not be hard for the minute forms of the organisms to pass through the vessel walls, and in fact evidence of this was seen in three cases, although on account of the hyaline character of the forms definite conclusions are impossible.

A fourth, and fairly frequent type of cortical lesion consists of the thrombosis of a vessel, with fibrin and blood cells in the lumen and a surrounding exudation of lymphoid, large mononuclear, and plasma cells, with formation occasionally of connective tissue. In these lesions organisms were never found. It is possible that they are the result of the occlusion of the vessel further on by the organisms, or the organisms may have been destroyed.

Distribution of the Brain Lesions.—As in the gross examination, the greatest numbers of intracranial lesions are in the frontal and olfactory lobes, and in the basal ganglia.

Degenerations.—Many of the small pyramidal cells, and a less number of the large ones, show evidence of slight degeneration;

the cells stain faintly, the Nissl bodies are not made out, often the nucleus is faint or invisible or shrunken and pyknotic, irregular in shape or elongated. The cell body at times appears shrunken, the cytoplasm irregularly stained. In the large pyramidal cells there is apt to be a clear zone around the nucleus, with irregular staining of the periphery. The polymorphous cells appear normal. In the medulla the ganglion cells appear more normal, but here the Nissl bodies are usually not made out and the cell body is occasionally shrunken. The ganglion cell changes are more marked in the frontal region. Here especially ganglion cells are often seen with two to four trabant cells about them. Marchi stains show a slight diffuse deposit of osmic acid in the myelin sheaths throughout the brain.

Miscellaneous Lesions.—The third ventricle shows lesions in the choroid plexus of the velum interpositum similar to those in the meninges, except for the absence of necrotic areas, and a larger proportion of phagocytic endothelioid cells. One foramen of Munro is partially occluded with a perivascular lesion. Sections of the lateral ventricles show similar conditions in the choroid plexus.

Distribution of Basal Ganglia Lesions.—In the gray matter of the median thalamic nucleus are many small lesions, the largest about 0.1 mm. in diameter, for the most part of the non-reactive type. In one section 5 by 8 mm. in size, twelve small lesions are found. The vessel sheath spaces are often greatly dilated and contain plasma cells or lymphocytes.

Peripheral Nerves.—Organisms are packed beneath the nerve sheath of the eighth cranial nerve and are in the capillaries of the same cranial nerve.

Aqueduct of Sylvius.—Sections of the occluded aqueduct show a mass of chronic inflammatory tissue with much vessel formation, similar in general character to the meningeal thickening, and containing many organisms, which completely fills the lumen. The wall of the aqueduct is thickened with glia tissue.

Ventricles.—About the ventricles there is a dense gliosis.

Spinal Cord.—There is slight meningitis of the same character as in the cerebral meninges.

Lungs.—In most sections there is a typical acute bronchopneumonia in which no torula organisms can be found. Section of the left lower lobe shows a pneumonia with alveoli filled with polymorphonuclear leukocytes, red blood cells, lymphocytes, endothelioid cells, and fibrin.

Liver.—No lesions. A slight thickening of the portal connective tissue.

Spleen.—There are many nodules the size of miliary tubercles, composed of epithelioid cells with poorly staining nuclei and a few small giant cells. Although there is no central caseation the nodules closely resemble the more chronic type of miliary tubercles. There is sometimes some central necrosis. The nodules are scattered throughout the tissue without reference to the follicles. No organisms of any kind can be found in these nodules. The arteries of the follicles show hyaline degeneration, and there is slight hyaline in the reticulum.

Kidneys.—A chronic lesion, about 2 mm. in diameter, composed of a diffuse interstitial infiltration with lymphoid and plasma cells, without caseation, occurs near the pyramids. In giant cells and free are organisms which stain faintly and are evidently partially destroyed. Other lesions consist of small accumulations of lymphoid and plasma cells, without visible organisms, in the renal cortex. Degeneration of near-by tubules is evident.

Heart.—No lesion. Histological changes probably postmortem in origin. Sections of the mitral valve show organized vegetations and cicatricial connective tissue.

Adrenals.—No lesions. Postmortem changes only.

Bronchial Lymph Node.—A small amount of carbon deposit, a diffuse increase in connective tissue, a somewhat thickened capsule, and hypoplastic germinal centers.

Ovary.—Some areas of hyaline connective tissue occur and there are collections of large pale cells.

A. Discussion of Case I.

Explanation of the Clinical History.—Evidently the internal hydrocephalus, to be explained by the stoppage of the aqueduct of Sylvius by chronic inflammatory tissue, together with the chronic meningitis, is sufficient to explain the general pressure symptoms of long duration. The effect of the long continued pressure explains in part the cerebral symptoms; the more localizing symptoms in the frontal lobes, basal ganglia, cerebellum, and cranial nerves are to be further explained by the lesions in these regions found at autopsy. Lesions such as these, with their chronic course and variety of situation, are evidently capable of simulating brain tumors with definite localizations so closely that from the symptoms alone a differential diagnosis would be impossible.

That the organisms are the causal factor in the lesions is proved by the peculiar character of the lesions, by the occurrence of the organisms in all the lesions in enormous numbers, by their occurrence nowhere else, and by the absence of any other demonstrable agent. It is unfortunate that cultures could not be obtained and Koch's laws fulfilled, but experimental lesions have been produced by us in animals by torula organisms, which are so exactly like those of this parasite in morphology and in reaction that there can be no doubt that the organism found in this brain is a torula. The morphology of the parasite with the clear homogeneous appearance of the large ones, the small number of differentiated droplets in the small ones, the tendency to multiply in and dissolve cells, to produce solution of brain tissue with only a slight chronic reaction; the formation of a wide clear zone about the outer wall, demonstrated by special stains to be caused by a gelatinous deposit in the lesion which keeps the organisms far apart and becomes converted into threads connecting the organisms, and the good staining properties of the cell wall, all differentiate this organism distinctly from the oidium, which has a finely granular content separated from the wall by a clear zone, a faintly staining or non-staining cell wall, slight or no production of gelatinous material so that organisms lie close together, and a tendency to attract polynuclear cells and cause a proliferation of fibroblasts. This organism is distinct from the coccidioidal organism in the smaller size, the presence of budding, the absence of endosporulation, and in the failure to attract leukocytes. The case is one of torula infection and is closely similar clinically and pathologically to the cases collected from the literature.

How can the absence of reaction in the intracerebral lesions of long duration be explained? There is a reaction in the meninges, so that the lack of reaction in the brain cannot be due to the peculiar nature of the organism. In morphology the parasite is old and slowly growing, so that the lesions could not possibly be explained by an invasion near the time of death. Something prevents the reaction of the cerebral tissues, and the most probable substance which could do this is the gelatinous substance peculiar to these lesions. Probably this gelatinous deposit greatly hinders all attempts at destruction of the parasite by the host. The general gliosis cannot be ascribed to the action of the organisms, but is to be explained, for the most part at any rate, as the result of the long continued pressure due to the internal hydrocephalus. The resulting interference with circulation may also explain the degenerations found.

The solution of tissue confined to the immediate neighborhood of the organisms suggests that the poisonous products are very slightly diffusible or are neutralized immediately.

Whether the intracerebral lesions arose from the meningeal lesion by the carrying of organisms along the perivascular sheaths, whether the reverse occurred, or whether both occurred independently, it is impossible to say. No direct connection between a meningeal lesion and an intracerebral lesion was ever found, except in the case of the cerebellar lesion. We can only say that probably in many cases the infection extended by way of the perivascular spaces.

The resemblance of the meningeal lesions to tuberculosis is interesting. The chief differences between these lesions and those of tuberculosis are the absence of perivascular infiltration, the diffuse distribution of giant cells without reference to nodule formations, the large number of plasma cells in the tissue, and the occurrence of spaces in the giant cells and tissues filled completely or partially with organisms.

2. *Case II.*

The second case was that of a man, 39 years old, a teacher living in Boston, who entered the Surgical Service of the Peter Bent Brigham Hospital on Nov. 8, 1914. The history was complicated, and the diagnosis had been uncertain. The main symptoms were cerebral, and included a right hemiplegia, dizziness, and drowsiness, and a complex referable to increased intracranial pressure. The clinical record follows.

Family History.—Negative.

Past History.—A severe attack of scarlet fever at 3 years of age. Frequent colds with cough, but no chronic bronchitis, or chronic cough with raising of sputum. No history of hemoptysis. Syphilis and gonorrhea were denied. The highest weight was 180 pounds, 14 years before entrance; at entrance it was 170 (average weight). There had been no cardiac or gastro-intestinal symptoms. Nocturia occurred one or two times. There had been no edema. There was an error of refraction, for which glasses had been prescribed 7 years before entrance, without subsequent correction. The secondary sexual characteristics largely failed to develop. In March, 1914, an acute middle ear was opened and drained with good result.

Present Illness.—In the latter part of September, 7 weeks before entrance, pain in the right ear came on. The ear was opened and drained and a small amount of pus was obtained. The pain was relieved and for a week the patient felt well. 6 weeks before entrance a frontal headache began, with a temperature of 102°, and the patient went to bed. 3 days later, on awaking, he found that he had a right hemiplegia, affecting the arm most of all, then the face, and to a less degree the leg. The hemiplegia gradually cleared up, except for a residual weakness of the right arm. During this same period of 6 weeks drowsiness was a marked symptom, the patient sleeping most of the time during the day. There was no loss of vision.

The patient was at the Massachusetts General Hospital under the observation of Dr. F. T. Lord, from Sept. 21 until his admission to the Peter Bent Brigham Hospital. During his stay there two spinal punctures were made. The first one showed 57 cells (lymphocytes) per c. mm. The Wassermann test was negative, the Noguchi positive, the gold chloride test positive for tumor or tuberculosis. The second puncture fluid had 21 cells per c. mm. Here again the Noguchi test was positive and the Wassermann negative, but the gold chloride test was positive for syphilis. A Wassermann test on the blood serum was again negative. Cultures of the spinal fluid were made on blood serum, and no growth was observed within 48 hours. A guinea pig was inoculated with the fluid, and later killed, with negative results.

The eye grounds were negative on several examinations in September and the early part of October.

Salvarsan was given twice, first on Oct. 16, 0.1 gm., then on Oct. 23, 0.3 gm. Previous to the salvarsan, mercury inunctions were used for about 3 weeks. The night before the second administration of salvarsan the patient complained of headache. After the inoculation, fever, occipital and bitemporal headache, dizziness, and vomiting came on. The temperature soon went down, but the headache and dizziness persisted until entrance to the Peter Bent Brigham Hospital, and vomiting occurred three times without nausea. On Oct. 26 examination of the eye grounds showed an early choked disc without measurable swelling.

An x-ray of the chest showed a diffuse shadow at the roots of both lungs. The tibia had some thickening of the bone.

Physical Examination at Entrance to the Peter Bent Brigham Hospital.—A right-handed man lying in bed with his eyes closed, apparently from photophobia, complaining of pain in the eyes. There was evident weakness of the right face and arm, and some puffiness under the eyes. The veins of the upper lids were dilated and the globes were prominent. The head had no areas of tenderness or change in percussion note.

Cranial Nerve Examination.—Nerve I: normal. Nerve II: the ophthalmoscope showed in the right eye obscured margins on the temporal side, new tissue in the cup, and a disc raised 2 D. The left eye had a more advanced choked disc. There was a height of 3 D, with embedded vessels, and one punctate hemorrhage. The surrounding retina showed considerable edema; the visual fields were practically normal. Nerves III, IV, and VI: the pupils were irregular, small, and reacted sluggishly, especially on the left. No von Graefe's sign, no nystagmus. Movements of eyeballs not restricted. Slight exophthalmus, no diplopia. Nerve V: no subjective disturbance. Masseters and temporals equally strong. Pain, touch, and temperature well and equally recognized. Nerve VII: the right corner of the mouth was weak, and the right nasolabial fold smoothed out. The eyes closed and the forehead wrinkled equally well on both sides. Nerve VIII: a watch could be heard at 3 feet on each side. History of right hemiplegia. Air conduction was better than bone conduction on both sides. Galton whistle was well heard. Weber's test was heard, but not referred to either side. Nerve IX: no history of difficulty in swallowing and speaking. Nerve X: pulse regular, 64 to the minute. History of vomiting three times. Palate symmetrical. No vocal cord disturbance. Nerve XI: sternocleidomastoid and trapezius equally strong on both sides. Nerve XII: tongue protruded in median line. Movements normal; no apraxia. Except for the impairment of motor power on the right, there were no symptoms referable to the frontal, temporal, parietal, or occipital regions. Dynamometer test: right 10 kilos; left 70 kilos. All the muscle groups of the right arm were markedly weak. The right leg was not greatly impaired. There were no sensory abnormalities; no astereognosis. Cerebellar examination showed dizziness; no nystagmus; inability to stand on account of weakness, but no history of unsteadiness; impossible diadokokinesia on the right, normal on the left; finger to finger and heel to shin tests fairly well performed, allowing for weakness of the right arm and leg.

Reflexes.—The abdominal and plantar were absent on the right. The epigastric was not elicited. The cremasteric, plantar, corneal, triceps, and biceps were present on both sides. The knee jerks were active to exaggeration, especially on the left. The Achilles jerks were active on both sides. Clonus was absent on the left, poorly sustained on the right. Babinski and Oppenheim were absent.

Examination of the right ear showed a little clotted blood about the external meatus, a dark blackish green membrane with no light reflex, and a small scar at the center. The left drumhead was bulging a little and reddened around its margin, with dim reflex. X-ray of the head was negative. The urine had a specific gravity of 1,750; albumin 0; negative sediment. The white count was 9,100; hemoglobin 75 per cent (Talquist). The temperature was normal. Wassermann reaction on the blood serum was negative.

Positive Findings, Subjective.—Pain in the right ear, two attacks, in March and September, 1914. Impaired vision of 2 weeks' duration. Headache and fever for a few days 6 weeks ago. Right hemiplegia, beginning 6 weeks ago and clearing up partially by the time of entrance. Dizziness of 2 weeks' duration. Headache of 2 weeks' duration, located in eyes. Vomiting three times in the last 2 weeks, following the administration of salvarsan. Drowsiness of 6 weeks' duration.

Positive Findings, Objective.—Weakness of the right face, arm, and leg. Exophthalmos. Dilated venules of eyelids. Choked disc, more marked in the left eye. Sluggish pupils. Exaggerated deep reflexes, especially on the right.

Wassermann reaction (blood serum) negative.

Progress of Case.—On Nov. 13 a left subtemporal decompression operation was done to relieve the increased intracranial pressure. The dura was found to be quite tense, and there was considerable fluid. The arachnoid and brain surface appeared normal.

The wound healed quickly and well. At first the headache was less, but in a few days it returned and frontal symptoms, such as disorientation and loss of memory, with failure to recognize his family, became more and more evident. Suboccipital headache was then complained of. Drowsiness continued. By Nov. 21 the suboccipital headaches had become very severe, and disorientation and hallucinations were marked. Incontinence of feces and urine at night with great restlessness were noted by Nov. 25. The eye grounds showed no further changes. On Nov. 27 the headache seemed to be mostly frontal. Examination on this date showed a deviation of the jaw to the left. The disc swelling was 4 D, and the decompression very tense. Vomiting occurred occasionally. There was an inspiratory hiccough, and deviation of the tongue to the right. There were wrist clonus and ankle clonus on the right. On Nov. 30 some apraxia was noted. On Dec. 1 spinal puncture gave 15 cc. of fluid, not under increased pressure. There was 1 cell per c. mm. (lymphocyte), and about 60 red blood corpuscles. On the same day eye examination revealed a swelling of the discs of 4 D with exudate and edema spreading far over the retina. On the left were many flame-shaped hemorrhages. The tentative diagnosis at this time included temporal lobe abscess, unilateral hydrocephalus, rapidly growing glioma, or vascular lesions.

Operation.—On Dec. 4 an osteoplastic exploration was made. The brain was incised to a depth of 3 cm., in the posterior part of the field, and a needle inserted through this opening, through which about 150 cc. of cerebrospinal fluid were obtained. There was definite improvement following operation, but for only a brief period. Pulse and respiration became irregular. A ventricular puncture was made through the former opening, and 175 cc. of slightly turbid fluid were withdrawn, in which 1 cell was found per c. mm. A Wassermann reaction on the spinal fluid on Dec. 4 was negative. On Dec. 11, 200 cc. of ventricular fluid were obtained, and a Wassermann reaction on it proved negative. Following the puncture came relief of the suboccipital headache.

Ventricular punctures were made, with the following results:

Dec. 17.	150	cc. of	yellowish	fluid,	60	red cells.	
“ 22.	30	“ “	spinal	“	4	“ “	
	90	“ “	ventricular	“	18	“ “	
“ 27.	118	“ “	“	“	78	“ “	
Jan. 2.	130	“ “	“	“	84	“ “	3 white cells.

Examination of the fluid gave: albumin, 0.016 to 0.12; sugar, 0.0786 to 0.0972.

It is of interest that on Dec. 22 the spinal fluid soon ceased flowing, while the ventricle, punctured at the same time, continued to give forth fluid. This seemed to prove the absence of a free communication between the ventricle and the spinal subarachnoid space.

On Dec. 7 Cheyne-Stokes respirations were noted at times. The patient became more stupid and refused nourishment except milk. The pulse became irregular, there being a pause every 6 to 10 beats. On Dec. 8 the irregularity of pulse and respirations entirely disappeared, but returned on Dec. 11. On Dec. 12 paralysis of the right side was practically complete, and there was marked aphasia. On Dec. 28 there was difficulty in breathing, with rapid, noisy respirations. On examination of the lungs coarse râles were heard over the trachea.

After the last puncture there was the usual temporary relief of symptoms, and during the evening the patient seemed brighter than usual. The pulse was good, the respiration regular. The patient died during the early morning.

Autopsy.—The autopsy was performed 5 hours post mortem. The brain was hardened *in situ* by an injection of 10 per cent formalin through the carotid arteries.

Externally the body is that of a moderately well nourished man and shows no abnormalities other than a herniation of the brain in the left parietal region. No lymph nodes are palpable. There is no pigmentation of the skin. No scars are visible. The testes are large and firm.

The peritoneal cavity appears normal.

In each pleural cavity, at the apices of the lungs, are found a few string-like adhesions. The cavities are free from fluid.

The pericardial cavity appears normal.

Heart.—Weight 350 gm. The foramen ovale is patent to a diameter of about 4 mm., but the valve-like action of the folds of endocardium about it must have made the opening functionally unimportant. The valve segments all appear normal except for a very slight fibrous thickening of the edges of the mitral valve. On the aorta are several spots of sclerosis about 2 mm. in diameter. The coronary arteries show a slight sclerosis, but the lumen is fully patent.

Lungs.—The pleural surface of the apex of the right lung is deeply puckered with folds from 1 to 1.5 cm. deep. The upper lobe is shrunken and has a large area of consolidation, which cuts like hard fibrous tissue, and is composed of small, firm grayish white nodules varying in size up to 2 mm., not circumscribed, and set in a hard slate-gray tissue. The mass as a whole is irregular, with nodular extensions into the surrounding tissue. It is dry and anemic looking. The consolidation extends to the pleural surface and is surrounded by fibrous masses extending into the lung. There is no calcification, nothing even suggesting caseation, and no cavity formation. The bronchi pass into the fibrous area with dilatation and are lost in it. In the lung elsewhere are scattered small miliary nodules resembling those in the consolidated area, and on the pleural surface are a number of small flat nodules, not elevated, extending in pointed processes into the lung beneath. Some of these are in small masses.

The left lung shows a similar condition, but the consolidation is more extensive, and occupies most of the upper lobe, even to the root of the lung. The puckering of the surface is very marked.

The bronchial lymph nodes are enlarged, pigmented, indurated, but neither caseated nor calcified. The mediastinal nodes are similar to the bronchial, showing on section yellowish white areas.

Liver.—Weight 1,920 gm. The external surface and cut section appear normal. The bile passages are open and appear normal.

Spleen.—Weight 280 gm. When cut it is found to be soft, scraping off easily with the knife. The surface is deep red, with prominent Malpighian bodies.

Pancreas.—Appears normal.

Gastro-Intestinal Tract.—Appears normal.

Kidneys.—Weight of each 200 gm. The capsule strips easily, leaving a smooth deep red surface. On section deep congestion is seen, with prominent markings.

Adrenals.—Slight postmortem degeneration.

Bladder, Prostate, Seminal Vesicles.—Appear normal.

Aorta.—Slight diffuse sclerosis of the abdominal portion.

Head.—There is considerable adhesion about the site of the bone-flap operation.

The calvarium, on removal, appears normal, as does the external surface of the dura. When the removal of the brain is attempted, it is found that there are very strong adhesions in both cerebellar fossæ, which prevent the removal of the cerebellum without tearing it. There is no exudate here, however, or evidence of acute inflammation. A piece of the dura with adherent cerebellum is put into Zenker's fluid at once. The middle ears are opened. The right appears normal, the left shows a slight amount of mucoid material.

Brain.—There is a large bulging mass on the left side at the site of the decompression operation. The convolutions are flattened. The dura, except in the immediate vicinity of the wound, is not adherent. The pia is slightly thickened and cloudy, but hardly to a noticeable extent. On the upper surface of the cerebellum, particularly on the right side, but to a certain extent elsewhere, there is a very definite thickening of the pia arachnoid, which has stripped smoothly from the dura, but is firmly adherent to the cerebellum. The same thickening of the pia arachnoid with formation of adhesions is found posteriorly, more marked on the right.

The brain is then cut into parallel frontal sections from 3 to 6 mm. thick.

Section through the frontal lobe shows dilated ventricles and normal cortex. In a section through the anterior commissure there is found on the left side, just above the anterior commissure, in the lower extremity of the internal capsule, a lesion 4 by 2 by 3 mm. anteroposteriorly, yellow, soft, with loss of brain substance.

5 mm. further posteriorly, at the level of the amygdaloid nucleus and the anterior tip of the caudate nucleus, is a lesion 6 by 3 mm., extending 6 mm. posteriorly, consisting of an area of induration with a yellow soft spot in the center, situated in the globus pallidus and lower part of the internal capsule on the left.

A section through the head of the caudate nucleus shows greatly dilated ventricles. The dilatation is equal on both sides. The horizontal diameter of the ventricles is 2.2 cm., the greatest vertical diameter (measured diagonally) 3.3 cm.

At the level of the tips of the anterior horns of the ventricles the cortex of the superior frontal convolution is 2.5 to 3.5 mm. thick, of the midfrontal 2.5 mm., of the inferior frontal 3 to 3.5 mm., of the uncinate gyrus 1.5 to 2 mm.

In the lenticular nucleus on the right, and extending very slightly into the internal capsule, is an indurated pale area 4 by 2.5 mm. made up of several spherical nodules 1 to 2 mm. in diameter. It extends 9 to 10 mm. anteroposteriorly.

The third ventricle, the foramen of Munro, and the aqueduct of Sylvius are dilated. The brain stem appears normal. There is no evidence of change in the posterior lobes.

The brain is softened in the vicinity of the operation.

Cerebellum.—On section, in the left upper part, posterior to the dentate nucleus, is an area seemingly of purulent infiltration of the tissue, with a matting together of the cerebellar leaflets. The lesion extends into the cerebellar tissue and resembles tuberculosis strongly, but the definite caseation is distinctly absent. The lesion is more diffuse than a tuberculous lesion. On further section this lesion is found to extend posteriorly to the surface of the cerebellum. Another similar but smaller soft mass is found in the right upper posterior portion. It appears like a softening of the tissues, without a definite line of demarcation. Even after hardening it is soft. It extends posteriorly as does the other lesion, and in the posterior part cuts with much resistance, and appears like a meningeal process with extensions into the cerebellum.

No exudate can be seen on the base of the brain.

The spinal cord is removed, but is not observed to be abnormal in gross.

Microscopical Examination.

Cerebellum.—Section through the lower surface with adherent dura. The dura is greatly thickened by dense connective tissue, and is separated from the cerebellar cortex by a wide mass of chronic inflammatory tissue. On lower power observation it is seen that this tissue has areas of irregular shape where there are few cells and much connective tissue; occasionally these areas have an almost spherical form. Between the denser areas the tissue is thickly infiltrated with mononuclear cells. Some areas suggest tubercles; there is a central necrotic or almost caseous mass, with dense connective tissue about it. A prominent element in the tissue as a whole is the large number of giant cells, which are scattered about diffusely, but are more numerous in the denser areas. There are a few small collections of polynuclear cells, slightly larger than giant cells. In giant cells and outside of them can be seen clear spaces, in which small organisms are barely visible.

The cerebellar cortex is partially necrotic and replaced by this tissue, which extends into it in thin strands, so that the molecular layer has a shredded appearance, while the granular layer appears to be intact. High power observation shows that the necrotic areas have in the center caseous cell detritus, in which, especially near its edge, polymorphonuclear cell nuclear detritus and remains of the organisms to be described later can be made out. Directly bordering the necrotic area is connective tissue arranged in general radially, and containing occasional polynuclear, mononuclear, and plasma cells; the mononuclear cells here also contain the bodies. Giant cells are not especially numerous in this zone. Beyond is the main mass of granulation tissue.

The major part of this tissue is made up of connective tissue which forms a loose network in the meshes of which occur principally plasma and giant cells; lymphocytes occur in much smaller numbers, and polynuclear cells are still more rare, but are seen especially in small collections about the size of giant cells. Plasma cells with several nuclei are occasionally found. The giant cells are of two types. One variety has clear oval or spherical nuclei arranged along the regular definite border; the other has long spindle-shaped nuclei in parallel fashion, and long prolongations of the cytoplasm. The most striking feature of the giant cells is the spaces filled with the organisms.

Organisms.—In size they range from slightly over 1μ to 7.5μ. As in the preceding case, the large forms are spherical, with a wall about 0.75μ thick. The size of the most frequently occurring organisms is 4.5 to 5.5μ in the longest diameter; these forms are slightly ovoid, the diameters of two typical organisms being 4 by 5μ, and 3.5 by 5.5μ; some forms are so ovoid that they measure 2.66 by 4.66μ. The very small forms are often much elongated, measuring 1.5 by 2.75μ or 1.87 by 3.5μ. As in the previous case, the wall varies in thickness with the diameter of the organism, and it is impossible to make it out in the smallest organisms. They have the same general refraction as in the previous case; the wall of the large ones is outlined by a double line, and stains in the same way.

The chief difference between the organisms in this case and the first case is in the presence of a larger amount of staining material within the cell; this is to be explained largely on account of the fact that in the second case tissue was put into Zenker's fluid only 5 hours post mortem. In sections of the material preserved in formalin there is the same internal structure as in the previous case; that is, a few globules or droplets taking many stains slightly. In the Zenker material stained with aniline blue connective tissue stain, irregular red-staining masses or specks are seen. In the smallest organisms

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these masses are often elongated and slightly curved, and fill more than half the cell space, giving a sickle-like appearance. Often there are two or more separate masses, perhaps connected with a thin thread, or perhaps merely four or five little specks; but no appearance was ever traced out suggestive of a mitotic or amitotic division. In the slightly larger forms the masses occupy a smaller proportion of cell space and show much more variety in shape and arrangement. There may be a circular form with thickenings in the outline; or a long bar with curved cross bars, or a Y-shape or X-shape, or small specks. Occasionally the mass is round or oval, with one or two darker points, and apparently a membrane, and resembles a nucleus closely. Here again no correlation can be made out of changes in the chromatic material with the reproduction processes, except that when budding occurs the large organism sometimes contains the material in small masses, and some of the smallest of these apparently pass out into the bud. More often, a single large chromatic mass, containing practically all the chromatin of the cell, is seen at the budding end. As the bud forms the mass shows a concavity toward the cell interior, and a prolongation of the mass passes out into the bud and then breaks off as the bud separates. This corresponds in general with the changes found by Kohl in torulæ. In the large sized organisms, as in the previous case, chromatic material is slight or absent. The chromatic material stains with hematoxylin and with methylene blue, but as the latter stains the wall the same color it is not so useful for the study of the internal structure. It takes the Marchi stain, and the Scharlach R stain slightly, as in the previous case. With formalin tissue teased out in salt solution, with a drop of 10 per cent sodium hydroxide, the organisms stand out strongly from the tissue elements. Iodine cannot be made out to stain the cell wall.

Reproduction.—Definite buds are much more frequent than in the other case. The medium sized cells are the most active; the process consists of an extrusion of a part of the cell interior at one end, which, when it attains a diameter of 2.5 to 3.5μ, becomes separated from the parent cell by a constriction. The cell wall at first bulges out, then the part enclosing the bud becomes thinner as the bud enlarges, and often appears as a very delicate membrane. Sometimes very small cells are formed, with no visible wall. When small organisms divide, the bud is more nearly the size of the parent than in the other case. Sometimes a multiplication of the very smallest organisms by a bud the same size as the parent is suggested. The larger organisms bud rarely, but when they do they either send out a protoplasmic mass with an extremely thin membrane or bulge out the whole cell wall. Measurements of budding cells are as follows: a cell 4.25 by 5.5μ is connected by a thin isthmus with a cell 2.25 by 3.75μ; a cell 4.75 by 6μ has just become separated from a cell 2.5 by 3.75μ; a cell 4 by 5μ is connected by an isthmus 0.75μ thick with a mass 1.5 by 2.5μ.

Occurrence of Organisms.—More frequently than in the previous case the organisms partially fill spaces in giant cells, endothelioid cells, or tissue. Often one large organism is seen near the center of a space, with many small ones about the periphery; probably the giant cell took up one organism, which produced another cell by budding, and then by continued budding a small colony was produced, with continued enlargement of the cavity. The original organism becomes large and thick walled, representing an involution form or resting cell. Earlier stages of this process are easily found; in one case a medium sized organism in a giant cell surrounded by a thin space was pushing a bud into the protoplasm of the cell. Occasionally organisms lying in a space are connected by a thread exactly similar to the filaments seen in the previous case, and evidently caused by a drawing out of material about the cells as they separate.

Relations of the Organisms to the Cells.—The organisms have the same destructive effect upon the giant cells as in the previous case. The frequency of budding within giant cells shows even less evidence of ability of the giant cells to harm the organisms. Whether the vacuole in which the organisms lie is a digestive vacuole or whether it represents a lytic effect of the organisms upon the cell cannot be determined definitely. As other tissues are definitely dissolved, and as the vacuole enlarges until the cell disappears, it is possible that it does represent histolysis of the giant cell by the organisms.

There is a definite lytic effect of the organisms upon the cerebellar cortex. Organisms are seen in the outer parts of the molecular layer, and the tissue about them becomes loose and full of spaces, in which plasma cells and then fibroblasts appear.

The cerebellar cortex reacts by the production of a definite gliosis, with heavy glia fibers, which extends into the granular layer. The Purkinje cells next to the lesion show marked chromatolysis and often appear as oval bodies with fine blue granules scattered diffusely through a coarse pink protoplasm, no nucleus being visible.

Sections of the Extensive Areas of Softening within the Cerebellar Leaflets.—There is necrosis of all layers of the cerebellum, with the formation of large masses of necrotic or caseous material and loose collections of lymphoid and large phagocytic mononuclear cells. The latter have finely vacuolated, faintly staining cytoplasm and small round eccentric nuclei, and usually contain organisms. The necrosis often is in great masses, in which few nuclear remains and many hyaline organisms can be made out. There is occasional hemorrhage but no fibrin formation. Large collections of polynuclear cells sometimes border regions of necrosis. Caseous or necrotic areas sometimes touch seminecrotic cerebellar tissue without intervening inflammatory tissue. In a few places, just outside of the cerebellar border, a moderate number of large epithelioid cells are seen. Rarely, next to the cerebellar tissue many necrotic polynuclear cells occur. The cerebellar cortex, in undergoing destruction, becomes vacuolated, especially at the level of the Purkinje cells, the nuclei become further and further apart, and the tissue is more and more indefinite, until it can no longer be recognized as brain tissue. Sometimes there is enormous enlargement of the molecular layer, with separation of nuclei, without definite vacuolization. Mononuclear cells often are present in the vessel walls, and about the vessels there is often a thick plasma cell infiltration. In the midst of the caseous areas vessels often have an intima and media greatly thickened from cell proliferation. There is occasional slight proliferation of the adventitia.

Formation of Large Mononuclear Cells.—The glia cells in the molecular layer become swollen, the cytoplasm faintly staining, and in fine network formation. The cells show some irregularities in form and in distribution, become more numerous near the outer part of the molecular layer, and then crowd the tissue outside. Organisms are often present within them and are apparently destroyed with them, becoming faintly staining and scarcely visible.

Intracerebral Lesions.—Sections from the border of the internal capsule on the right show two lesions between white and gray matter, extending into each, but chiefly into the gray matter. One lesion has two areas of caseation similar to those in the meninges, surrounded by tissue similar to the chronic inflammatory tissue of the meningeal lesion. There is also a spherical accumulation of giant, lymphoid, and connective tissue cells, without central necrosis, containing many organisms in cells and spaces and surrounded by dense connective tissue. The giant cells contain many organisms which destroy their protoplasm, producing spaces which give the dense tissue a vacuolated appearance. There is more dense connective tissue in this lesion than is usual in the meningeal lesion. Where it borders on the brain tissue the lesion is thickly infiltrated with plasma cells and lymphoid cells. The brain tissue near the lesion is either vacuolated or compressed, but shows little cell increase. The other lesion is close to the first and consists of three partly coalescent nodules without necrosis, of similar construction to those just described. In both lesions there is a thick plasma cell layer along the vessels. In neither is there any great infiltration with the large phagocytic mononuclear cells. About both lesions is an increase in glia cells with a slight formation of thick glia fibrils. The ganglion cells show chromatolysis, with eccentrically placed nuclei, and often are indented by glia cells. Occasional organisms can be seen in the loose cerebral tissue about the lesion.

Sections from the left internal capsule also show two lesions separated from each other by nearly normal brain tissue, situated chiefly in the white matter of the internal capsule. The larger lesion has ovoid accumulations, with necrotic polynuclear cells and organisms in the center, and a wall similar to that of the nodules previously described, containing, however, a rather greater number of organisms and showing a more extensive necrosis. Here the organisms are larger and more spherical than elsewhere, are more uniformly distributed throughout giant cells without definite space formation. On the whole, they appear nearly identical with those in the meningeal lesions of the first case. Often each organism has an eccentric red-staining round dot. The giant cells in this nodule are almost entirely converted into thin rims containing a little vacuolated protoplasm between large numbers of organisms. The tissue about this lesion and the nodule near it is like that previously described. Near the lesion, in the white matter, are ill defined areas, where brain tissue is lacking, and the space is filled with large mononuclear cells. No organisms occur in these areas; they may be areas of degeneration resulting from the lesions or areas in which the organisms have disappeared. There is a slight gliosis about these lesions.

Sections of the cortex from the frontal, temporal, parietal, and occipital regions, and from the uncinate gyrus show, as a rule, no meningitis. There is a peripheral gliosis of moderate degree, very marked in the depths of the sulci. The increase in glia fibers extends almost to the ganglion cell layer, but is marked only in the subpial layer.

In sections of the occipital lobe there is a very marked meningeal thickening in one sulcus. The character of the lesion is in general like that in the cerebellum; but there are more minute collections of polynuclear cells. On one side of the sulcus the inflammatory tissue is making extensions into the brain tissue exactly as it does into the cerebellar cortex, but on the other side there is a very thick peripheral layer of glia fibers, through which no progress is made.

Sections from the temporal lobe show a marked peripheral gliosis, but no meningitis. The ganglion cells here appear slightly shrunken; the Nissl bodies are indistinct, and often a phagocytic glia cell indents the margin. This section also takes in the lateral border of the lateral ventricle, which has a very marked peripheral gliosis consisting of a dense felt of heavy fibers.

The anterior and posterior central regions on the right show edema of the meninges with a slight increase in mononuclear cells, and occasional small organisms. Gliosis and ganglion cell changes are much the same as in the temporal region. The anterior and posterior regions on the left are similar to those on the right. The frontal lobes also have some chronic thickening and edema of the meninges. Gliosis and ganglion cell changes are as in other regions. The uncinate gyrus shows the usual changes. The fourth ventricle and the aqueduct of Sylvius show a heavy gliosis. The choroid plexus appears normal. The spinal cord shows no meningitis. There is no peripheral gliosis.

Weigert stains show interruption of the tracts of the internal capsule on the left by the lesions, with degeneration of myelin sheaths near the lesion, manifested by swollen and bulbous fibers. The internal capsule on the right at the same levels appears normal. The internal capsule lesion on the right is very slight, and interrupts only a few fibers. Sections of the internal capsule at the level of the posterior end of the thalamus show isolated areas of degeneration or absence of myelin sheaths on the left side, the myelin sheaths being replaced by glia cells and fibers. Sections of the spinal cord show a distinct thinning with swelling and degeneration of fibers in the direct pyramidal tract of one side and the crossed pyramidal tract of the opposite side. Sections of the left optic and olfactory nerves appear normal. Bordering the ventricles and in the cerebellum there is degeneration of myelin sheaths, especially near the cerebellar lesions.

Marchi stains show marked deposit of osmic acid in the same areas where the myelin sheath stain showed degeneration. There is also much fat in and about the lesions.

Lungs.—There are large dense fibrous formations of hyaline connective tissue with few nuclei, tending to arrange themselves in large nodular whorls. No tendency is seen toward necrosis or caseation. Bordering the areas are small nodules consisting of lymphoid and endothelioid cell accumulations, with giant cells and connective tissue proliferation, closely resembling tubercles, but lacking caseation. Occasionally there is a slight deposit of brown pigment in the tissue. The near alveoli are filled with plasma and lymphocytic cells, with occasional large phagocytic endothelioid cells and giant cells diffusely distributed. The capillaries are increased in number and size. The giant cells are partially honeycombed with small round or oval spaces, which sometimes coalesce and contain indefinite brown granules in their centers. The appearance is what might be expected as an end-result of an infection of the same character as that of the meninges, but it is possible that it represents merely a form of degeneration. Certain of the giant cells contain radiate or stellate masses lying in a vacuole in the cell which are evidently of the same character as the stellate bodies described by Wolbach in giant cells in the spleen.

Other sections show nodular connective tissue thickenings surrounded by nearly normal alveoli. In these indurated areas are spherical formations where the tissue is loose and occupied by large irregular giant cells and a few lymphocytes and plasma cells. A later stage shows these nodules entirely converted into connective tissue, with no caseation, but with a surrounding lymphocytic and plasma cell proliferation. In these lesions are a few spherical bodies 4 to 6μ in diameter, with walls 1μ thick, and small central bodies containing central dots. In size and in the character of the wall they correspond with the torulæ found in the brain, but they differ in the absence of the gelatinous capsule and all evidence of multiplication. They probably represent organisms completely obsolete which have become enclosed in the dense connective tissue of lesions which are themselves obsolete. It was the presence of these bodies seen in a frozen section of the lung which first led to the consideration of this case as a possible torula infection.

Bronchial Lymph Node.—Similar connective tissue formations to those in the lung occur in the lymph nodes. Small and large areas of hyaline connective tissue of irregular shape are scattered throughout the node. The first formation of connective tissue takes place about the vessels and in the walls of the lymph sinuses. There are no collections of endothelioid and plasma cells, and no giant cells.

Kidneys.—Slight acute degenerative lesions.

Liver.—One nodular lesion the size of a miliary tubercle consists of giant, lymphoid, and endothelioid cells, embedded in connective tissue with lymphoid infiltration about the periphery.

Spleen.—There are nodular accumulations of endothelioid, lymphoid, and giant cells without caseation. Apparently later stages show hyalinized connective tissue, sometimes slightly infiltrated with lymphoid cells. These lesions usually occur in the follicles, and occasionally can be seen to arise around vessels. In general there is increased connective tissue about the vessels.

Adrenals, Pancreas, Myocardium, and Thyroid.—Negative.

Testicles and Seminal Vesicles.—Normal.

Cultures.—Cultures were made in bouillon of ventricular fluid removed during life. Smears showed round bodies considered to be precipitated stain, or other indefinite material. Nevertheless, the bouillon culture was inoculated into two white mice intraperitoneally under aseptic precautions. About 4 weeks later the mice were autopsied. Nothing was observed in gross. Microscopical examination of the tissues showed a meningitis consisting of a production of large phagocytic mononuclear cells in which occurred large and small organisms similar to those in the original case. The organisms were multiplying by budding. Some large forms 10μ in diameter occurred. Small forms of 2.5μ were seen. The organisms were nearly spherical, and had a few vacuoles in an otherwise almost homogeneous interior. The large organisms occurred surrounded by wide clear zones, in which radiating lines could be seen in some cases, like those in the first case and in Rusk's cases. In several cases extension into the cortex by solution of tissues without reaction was evident,—early stages of lesions similar to those in the preceding case. A large part of the meninges was edematous, with many organisms, some of them thick walled, but with no cellular infiltration. This is a condition like that of the second case (Rusk's) in the literature. No lesions occurred in other organs.

A. Discussion of Case II.

The chief differences between this and the preceding case depend upon the variations in the extent and activity of the process. In this case the process is so extensive that more necrosis and caseation result; it is so active that budding forms are frequent, and the organisms have not produced the large resting cells or the peculiar brain lesions especially associated in the first case with the presence of the resting cells. The characteristic tendency to solution of tissue is present, the meningeal inflammatory tissue is like that of the preceding case, and the absence of the peculiar intracerebral lesions is made up for by their presence in the brain of the inoculated animal. The difference between this case and those of coccidioidal granuloma or ordinary blastomycosis is obvious; further evidence for its identity with torula will be given under experimental results.

Explanation of the Clinical Course.—Underlying the general pressure symptoms of headache, vomiting, and impaired vision, with the corresponding objective findings, is an internal hydrocephalus, as in the other case. The mechanism here must have been partial blockage of the exit of cerebrospinal fluid from the foramen of Magendie by the dense inflammatory tissue. The hemiplegia is well explained by the lesions in the internal capsule, partly old and healed, partly active, with the resulting degenerations. The relation of the otitis media to the disease has not been discovered.

The lesions in the lungs, bronchial lymph nodes, liver, and spleen are in all probability due to the action of the same organism. The lesions are unusual, and bodies occur in the lung lesions closely resembling the organisms. Animal experiments show all stages to the production of the cicatricial lesions.

In this case again there is a close resemblance of the lesions with caseation to tuberculosis. There are the same points of differentiation; in this case the predominance of plasma cells is even more marked.

In connection with the data of all the cases of torula infection, it is interesting to observe additional points. Fever was noted in all but the first of the cases in the literature, where its presence or absence is not mentioned, and in Rusk's first case. In our two cases fever occurred only near the time of onset and was moderate in degree. In all cases where the white count was taken it was not increased, but usually fever was not present at the time. However, in Türck's case the white count was 7,000 when an irregular temperature was run. In ordinary systemic oidiomycosis there is usually a marked leukocytosis, averaging 16,000, and occurring up to 30,000. In our second case and in Rusk's second case there was a positive Noguchi reaction in the spinal fluid. Organisms were found in the spinal fluid in von Hansemann's case; in the spinal fluid and ventricular fluid in Türck's case; and they were evidently present in the ventricular fluid in our second case. In Rusk's cases and in our first case no examination was made. In Türck's case and in our second case cultures did not succeed.

The best means of diagnosis, until some exact serum test is worked out, will be cultures on agar or potato at room temperature, and inoculation of white mice or rats intraperitoneally with spinal or ventricular fluid or cultures, with microscopical examination of the brain. Some ordinary laboratory animals, such as guinea pigs, are practically insusceptible to the disease, and the usual technique of growing cultures for 48 hours on blood serum at incubator temperature must result in many failures; the organism grows much more surely on agar or potato at room temperature, and growth is often slow, especially after the organism has been passed several times through animals. Differentiation in smears from tissue elements such as red cells is best effected, as in oidiomycosis, by examining in salt solution or glycerine or with the addition of a drop or two of sodium hydroxide. In the ordinary stained smears recognition might be difficult.

The symptomatology of the cases resembles closely that of brain tumor. The essential factor in the similarity is the occurrence of a chronic, slowly progressing inflammatory process, which by being situated in such a way as to interfere with the passage of cerebrospinal fluid causes an internal hydrocephalus, or results in the formation of masses of parasites in various parts of the cerebrum or cerebellum, or causes a chronic meningitis with overproduction of fluid. Involvement of special nerves may give false localizing symptoms. The absence of cutaneous or recognizable systemic lesions adds to the confusion. The pathological reports of other cases of pseudotumors are so scanty that it is impossible to tell whether many of them may not have the same or a similar explanation. Pseudotumors have been one of the mysteries of brain surgery; an explanation of a few cases now gives a definite line of attack for future work. Necessarily there are also points of similarity with chronic diseases of the nervous system, such as syphilis.

IV. CLASSIFICATION OF THE DISEASES FORMERLY CALLED BLASTOMYCOSIS.

Botanically torulæ form a group of organisms similar to the yeasts in the form and organization of the cell and the method of reproduction by budding, but different in the constant absence of endospore production and the frequent lack of power to ferment sugars. Other points of difference are commonly present, but not invariably. From the oidia they are distinguished by their absence of mycelium production under all circumstances. The true yeasts are classed in most systems as ascomycetes on account of the endospore production. The real biological relationships of the yeasts and torulæ are not yet determined. The type of organism budding in tissues and producing mycelium in cultures is botanically an oidium. The oidia have no characteristic fructification and hence their systematic position is also obscure.

Coccidioides immitis is definitely an ascomycete on account of its endosporulation, and is seen to be in close biological relation to the yeasts.

The various organisms belong to different groups and have different appearances and pathological effects. Coccidioidal granuloma is already established as a name for the disease produced by the ascomycete with hyphæ, and causes no confusion. The term blastomycosis, however, which signifies a disease caused by a budding organism, obscures the real differences in the various diseases which have been included under its name, and should be discarded. Oidiomycosis, yeast infection, or torula infection should be substituted, according to the case. Following is a summary of the differential points in torula infection, oidiomycosis, and yeast infection.

Summary.—1. True yeast infection, produced by an organism which reproduces by budding. It produces no true mycelium, forms endospores under certain conditions, and usually ferments sugar. The organism is rather feebly pathogenic for animals. There are two authentic cases in man, the first being Busse's. Both cases include skin lesions. The pathological changes are characterized by necrosis, stimulation of epithelial growth, some exudation of polynuclear cells, tendency to giant cell formation, nodular accumulations of small round cells, and abscess formation. The organism has an adventitious capsule occasionally in human and animal lesions, but does not produce a gelatinous matrix and does not have even a capsule in brain lesions in animals.

2. Torula infection, produced by a yeast-like organism, distinguished from yeasts by its absence of endospore production under all circumstances. It never produces mycelium, usually does not ferment sugar, and reproduces by budding alone. The organism is more pathogenic for animals than that of the preceding group. The first spontaneous case reported was described by Frothingham as occurring in a horse. Six cases are known in human beings. In localization the nervous system especially is affected, to a less extent other organs, never the skin as part of the general infection. The symptoms

are chiefly caused by the brain lesions. The pathological changes in the meninges are characterized by chronic inflammatory reaction, with areas of caseation like tuberculosis, if the lesion is extensive; the organisms usually occur in cells, bud freely in the large vacuole enclosing them, and usually destroy the cells. The organism produces peculiar intracerebral lesions, consisting of a lysis of the cerebral tissue, with only a very chronic proliferative reaction which is often almost lacking, and fills the lesion with a peculiar gelatinous material holding the organisms separate, in which occasionally threads and star-like processes form. In other organs it produces, as a rule, nodular lesions resembling miliary tubercles which finally become dense connective tissue masses. The organism in tissues has a nearly homogeneous, non-granular, faintly staining interior except in the smaller forms, varies in size from 1 to 13μ, and often produces large resting cells. The wall stains easily and diffusely. The organism increases by budding. Small buds may be produced by organisms of any size. When produced by an organism of small size they may equal the size of the parent. The small forms have a good deal of chromatic material in masses. In mice and rats pure cultures produce lesions of the same character as those found in man.

3. Oidiomycosis is caused by an organism reproducing by budding in tissue, and forming mycelium in cultures. There is no endospore production. There are over thirty recorded cases of systemic involvement, and more numerous cutaneous cases. In localization oidiomycosis affects especially the skin and subcutaneous tissues, no reported systemic cases being free from such involvement; it often involves bones; it affects all internal organs, including the brain, but has not yet produced lesions in the brain which have caused symptoms until just before death from the general infection. The pathological changes are characterized by necrosis and overgrowth of epithelium with miliary epidermoid abscesses, forming characteristic skin lesions; abscess production is present in deep tissues and in organs, also tubercle-like nodules; there is a marked attraction for leukocytes (except in occasional cases in the spleen and bone marrow); no lesions have the peculiar gelatinous matrix (although occasionally, especially in the bone marrow, an adventitious capsule is produced). The only reported case of meningitis was a purulent one; the brain lesions are

much like the other lesions with somewhat less reaction. The organism in tissues has a granular interior, usually with a separation of the protoplasm from the wall by a distinct space, is spherical, and reproduces by budding. The wall stains with difficulty or not at all. It is from 3 to 30μ in diameter, the average size being 16μ. In animals it produces lesions with difficulty; they resemble the lesions in man.

V. EXPERIMENTAL.

1. *Materials and Methods.*

All inoculations were made with pure cultures suspended in sterile salt solution. The organisms with mycelium were teased into as fine particles as possible. The site of each inoculation was shaved, washed with alcohol, and painted with iodine. We used the following organisms: a culture of torula from Frothingham's case of infection in a horse, a culture of oidiomycosis from the human cutaneous case reported by Wolbach, and a culture of *Coccidioides immitis* from a human case of coccidioidal granuloma.

Since so much experimental work has been done on so called blastomycetes and *Coccidioides immitis*, our results, which confirm the differences in the two organisms, will be given with especial reference to the histological changes rather than to the morphology of the organisms in the tissues.

2. *Experiments on Dogs.*

A thick suspension of each organism was injected into a dog intravenously to the amount of 5 to 8 cc. Later a similar suspension was injected into the lower bronchi through a rubber catheter introduced into the trachea. The animals were killed in 3 to 6 weeks. The dogs inoculated with oidiomycosis and coccidioidal organisms showed no lesions. The animal inoculated with torula had no lesions in any organs but the brain and kidney. The kidney showed a few minute white dense spots, about 1 mm. in diameter, in the medulla. On serial section of the brain hardened in formalin several small white areas 1 to 2 mm. in diameter were found in the cortex, white matter, and basal ganglia.

Microscopical Examination. Kidney.—The lesion consists of a diffuse collection of lymphoid and plasma cells with a few polynuclear cells, obliterating and replacing tubules. Plasma cells predominate. Other lesions consist of a diffuse connective tissue formation, with areas of plasma cells. No definite organisms can be found in these lesions. The lesions resemble closely those in the kidney in the first case.

Brain.—The lesions consist of focal collections of mononuclear cells with rare polynuclear cells. Some of the cells are plasma cells; most of them have a large amount of cytoplasm and large round centrally located nuclei, and appear to be arising from the glia cells about the lesion. A few large mononuclear cells are seen. Polynuclear cells are extremely rare. Some of the lesions are near vessels, and about the vessels there are dense masses of lymphoid cells. A few partially disintegrated organisms are found in these lesions.

These few experiments show that the dog must be regarded as a relatively resistant animal to the three groups of organisms. It is interesting that the only lesions in the series of dogs are brain and kidney lesions from the torula injection, and of these the brain lesions are the most numerous.

3. Experiments on Rabbits.

One series of rabbits was inoculated intraperitoneally with 2 cc. of a thick suspension of each organism, another intravenously in the ear vein, one subcutaneously, and one subdurally. With oidiomycosis no lesions were produced. The subdural inoculation with the coccidioidal organism resulted in an abscess at the site of inoculation from which a pure culture of the *Coccidioides* was obtained. In the rabbit inoculated intraperitoneally with the torula, lesions were found in the kidney, brain, and meninges.

Rabbit 1.—Intraperitoneal inoculation with torula. Animal autopsied 3 weeks later. In gross no lesions were noted.

Microscopical Examination. Liver.—A large area is found nearly the diameter of a low power field, with central caseation, surrounded by epithelioid cells, then a zone of thick infiltration with lymphoid cells, containing many eosinophilic cells, with a slight surrounding connective tissue band. No organisms are found in the lesion.

Brain.—A chronic meningitis in which definite torula organisms are found. The cells consist chiefly of large mononuclear cells and sometimes contain organisms. There are moderate numbers of plasma cells, but no polynuclear cells. The organisms are scarce and show much degeneration. The large phagocytic mononuclear cells are filled with hyaline droplets or vacuoles. The cortex near the lesion has a slight increase in glia tissue, with spider glia cells. In the cortex are focal lesions consisting of accumulations of mononuclear, lymphoid, and plasma cells, the lesions being about the diameter of a high dry power field. Organisms occur in these lesions but are difficult to find. The meningitis is not found in all sections.

Rabbit 2.—Subcutaneous inoculation with *Coccidioides immitis.* Autopsy 7 weeks later. A nodule 1 cm. in diameter was found at the site of inoculation open, with a thick purulent content. No internal lesions. Sections of the nodule show diffuse connective tissue increase and many large irregular masses of polynuclear cells, with little necrosis.

The intervening connective tissue is remarkably free from cellular infiltration. The abscess contents consist practically entirely of polynuclear cells. The border is sharp and made up of a band of denser connective tissue. Caseation occurs near the borders of the abscesses, rather than in the contents. No giant cells are present. The earliest lesions consist of small accumulations of polynuclear cells with surrounding connective tissue proliferation. The organisms occur in the abscess and in the connective tissue. They are placed close to the cells without intervening spaces.

Rabbit 3.—Subdural inoculation with *Coccidioides immitis.* At the site the meninges are greatly thickened with increased connective tissue and abscess formation. The lesion has extended into the cortex and is bordered there by a zone of connective tissue thickly infiltrated with plasma cells and lymphocytes. Outside of this connective tissue band polynuclear infiltration becomes more marked and large abscesses are found similar to those in the subcutaneous nodule just described, but more extensive, and with more necrosis and peripheral caseation. Giant cells occur frequently at the borders of the abscesses. The organisms occur in giant cells and free, but they never have a clear zone about them. They are seen more often outside than in the abscesses. Sporulating forms are rare. One large abscess has several free pieces of cortex within it. In the series of rabbits the tendency of the torula to infect the nervous system is evident. In one case a meningitis is produced from intraperitoneal injection. The coccidioidal organisms produce brain lesions only from subdural inoculations.

4. *Experiments on Guinea Pigs.*

Inoculations were made intraperitoneally and subdurally. No lesions were produced with oidiomycosis. With torula the only lesions produced were peritoneal nodules in the guinea pig inoculated intraperitoneally. The surface of the peritoneum was slightly dull and dotted with minute, raised, slightly whitish areas, appearing much like a culture of streptococcus on agar. Microscopically the lesions consisted of lymphoid and endothelioid cells in connective tissue with a few mono- and polynuclear eosinophils. The large resting cell forms of the organism occurred in the nodules singly, each organism surrounded by a clear space, about which were endothelioid cells which showed signs of fusion into giant cells. The muscle fiber just underneath the nodules showed a loss of the cross-striation so plain elsewhere.

Two of the guinea pigs inoculated with the coccidioidal organisms had lesions; the one inoculated subdurally had a brain lesion.

Guinea Pig 1.—Inoculated intraperitoneally with *Coccidioides immitis*. At autopsy abscesses are found in the testes, epididymis, and liver, and nodules in the peritoneum. There are no lesions in the central nervous system. The lesions consist of abscesses, large and small, and collections of epithelioid cells, as in the preceding case. The small circumscribed collections of polynuclear cells about a few organisms are frequent. Caseation is always in the zone about large collections of polynuclear cells. In the giant cells the organism enlarges until it finally appears closely surrounded by a thin band of the protoplasm and nuclei which appear unchanged. Organisms sporulate much more often than in the rabbit, and the leukotactic influence of the young organisms is very plain.

Guinea Pig 2.—Inoculated intraperitoneally with *Coccidioides immitis;* killed in 4 weeks. Lesions in the peritoneum, testes, epididymis, liver, spleen, and lung. There are no brain lesions. Pure cultures of the coccidioidal organism recovered from the testicular lesion. The lesions are similar histologically to those in the previous animal.

Guinea Pig 3.—Inoculated subdurally with the coccidioidal organisms. At autopsy an abscess is found at the site of the inoculation, from which a pure culture of the coccidioides was recovered. No lesions in the other organs.

Microscopical Examination.—Large and small masses of polynuclear cells, with surrounding connective tissue often infiltrated with polynuclear cells, have greatly thickened the meninges in and about a sulcus, compressed, and in one place invaded the surrounding cortex. A single mass of polynuclear cells is one and one-third times the diameter of a low power field. Organisms are numerous except in the thick connective tissue. Giant cells are rarely seen. Some small masses of polynuclear cells are surrounded by a zone of epithelioid cells. Where the lesion has eroded the brain there is much new vessel formation with exudation of polynuclear, plasma, and lymphoid cells, and in the brain all about the lesion there are polynuclear, plasma, and glia cells, sometimes forming thick masses. The meningitis is localized to the neighborhood of the sulcus.

5. *Experiments on Mice.*

Lesions were produced with the coccidioidal and the torula organisms, but not with that of oidiomycosis. The culture of oidiomycosis had been used previously in animal experiments, but had probably lost its virulence with time. The torula culture, which was just as old, seemed to have retained its virulence extremely well, for general lesions were easily produced in mice and rats. We were able, through the kindness of Dr. S. B. Wolbach, to procure paraffin blocks of the animals used in his experiments with oidia. The lesions found will be described briefly.

Coccidioides immitis Lesions.

Mouse 1.—Inoculated intraperitoneally with *Coccidioides immitis*. At autopsy a pure culture of the organism was obtained from a nodule in the liver and from a peritoneal nodule at the site of injection. Lesions were found in the mesentery, peritoneum covering the liver and spleen, and in the lung and liver.

Microscopical Examination. Lung.—Nodules consisting of many small organisms mingled with polynuclear cells. One mass consists of large organisms nearly all of which are sporulating, surrounded by a hemorrhagic zone containing a few polynuclear cells. Some lesions show little reaction other than hemorrhage; others large numbers of polynuclear cells and few organisms. Usually there is a beginning invasion of polynuclear cells and formation of connective tissue.

Liver.—There is a small collection of organisms with an early invasion of polynuclear cells. The liver tissue about the colony is compressed. Other larger lesions show diffuse infiltration with polynuclear cells and a connective tissue capsule. The liver cells immediately surrounding the colony appear normal except for compression. Other lesions consist of small abscesses containing small organisms and without surrounding connective tissue. Adherent to the peritoneal surfaces of the liver, spleen, and pancreas are large and small organisms with varying amounts of acute exudate. The mesentery is thickened with a purulent exudate and many organisms. There is a good deal of new vessel formation, and an infiltration in these places with plasma cells. There is necrosis, almost caseation, of organisms and cells in a diffuse manner. Peritoneal nodules occur with polynuclear cells, especially about small organisms.

The chief peculiarity of the lesions is the greater size of the large organisms, some of which measure 85μ in diameter, and the great frequency of sporulation, some lesions consisting of numbers of large sporulating cells producing masses of small organisms. The small amount of reaction about some lesions in the liver and lung seems to be due to the recent invasion of the tissue, for an acute reaction with hemorrhage is always present to some extent. Most of the lesions are fairly characteristic except for the small number of epithelioid and giant cells. The coccidioidal organism is a virulent one, and the infection evidently overwhelmed the animal.

Lesions with an Oidiomycosis Organism.

Lungs.—The bronchi contain a purulent exudate with organisms, and the walls are necrotic. Lobules of the lung are solidified with enormous numbers of oidia and a purulent exudate. It is difficult in these areas to make out the alveolar walls, which frequently appear to have been destroyed. Occasional small irregular areas of caseation are seen immediately surrounded by the infiltrated tissue and apparently the result of the crowding of the enormous numbers of the organisms in the tissue. The organisms lie close to each other or to the polynuclear cells, without intervening spaces. They are occasionally seen budding. Large endothelial cells occur and contain organisms, which distend the cells, but do not seem to injure them otherwise than by this mechanical action. There are a few giant cells in which organisms occur without causing solution of their protoplasm. No connective tissue formation is evident. Other large areas, normal except for a few large endothelial cells, immediately adjoin these lesions. About some of the vessels there is a plasma cell infiltration.

Lesions with Torula Organisms.

Mouse 2.—Inoculated intraperitoneally with torula. The peritoneum contains a slight amount of sticky exudate; the surface is dull, and small white thickenings are visible on the surface. The omentum and mesentery are thickened. No lesions can be found in the internal organs, except the brain. Pure cultures were obtained from the peritoneal exudate.

Microscopical Examination.—In the peritoneum are enormous numbers of very minute organisms and a few larger ones, appearing as empty shells which are often broken open. There is an infiltration with a few mononuclear cells and a moderate number of eosinophils. The organisms occur in spaces, some of which are fat spaces, others formed from destroyed cells. These spaces give the tissue a honeycombed appearance. In the omentum is a similar lesion with a slightly greater reaction, consisting of numbers of lymphoid, plasma, and large endothelioid cells. The brain shows a meningitis consisting of a considerable accumulation of large mononuclear cells in which no definite torula organisms can be found.

6. Experiments on Rats.

Inoculations were made intraperitoneally with the torula and oidiomycosis organisms. No lesions were produced with the oidiomycosis, but with the torula a general infection with lesions in the meninges, brain, and cerebellum was produced. Pure cultures of the organism were recovered from the animals in nearly all cases.

Rat 1.—Inoculated intraperitoneally with 2 cc. of a thick suspension of torula on Feb. 24, 1915. The animal died on Apr. 14, 1915.

Autopsy.—The peritoneal cavity contains no fluid, there are no adhesions, and no nodules on the peritoneum. The surface seems slightly dull and sticky. The abdominal organs and lymph nodes appear normal. The lungs are greatly distended, firm, pale grayish pink, with a slightly nodular appearance of the surface. All lobes of both lungs are affected in equal degree. On section the surface is whitish and sticky and slightly nodular. The tissue has a semitranslucent appearance. The brain appears normal.

Smears from the peritoneal cavity and lung show only torula organisms. In the smear from the lung there is much homogeneous material adherent to the organisms, staining faintly and obscuring the details. A culture from the peritoneal cavity gives a pure growth of torula. A lung culture gives a growth of torula, contaminated with other organisms.

Microscopical Examination. Lung.—The alveoli are dilated and often broken to form large spaces, which are filled with a gelatinous material in which organisms are embedded. With material fixed in Zenker's fluid the gelatinous material stains a faint reddish blue and is seen to be filled with fine granules taking a light red stain. There are irregular thickenings which stain blue and often take the form of threads joining the organisms. As a whole, the substance has shrunken during fixation, so that irregular spaces exist in it. With formalin fixation and hematoxylin staining the material is scarcely colored at all, but occasionally stains slightly where it is thickest. Cresyl blue after formalin fixation colors it intensely, however, and shows fine radiating thickenings from the large organisms. The larger organisms are spherical, 10 to 13μ in diameter, with a definite wall staining diffusely with methylene blue, which is often irregular in outline as if somewhat collapsed. The contents are homogeneous and stain faintly. The whole general appearance of the lesion and organisms is identical with that of the peculiar cerebellar and cerebral lesions of the first case. On close examination enormous numbers of small organisms varying in size from 1 to 6μ in diameter are seen. These occur especially in spaces surrounded by fragments of the destroyed cells of the alveolar walls. The method of reproduction is always by budding; medium sized organisms give off small buds 1 to 2μ in diameter, and organisms 3 to 4μ give off the smallest forms. Occasionally, the small forms appear to reproduce by buds the size of the original organism. These small forms are more oval than the larger ones and appear exactly like those in the second case except that they are not quite so thick walled and are not so frequently seen budding. They show the same relations to cells, multiplying freely in large vacuoles in giant cells, and finally destroying the cells. They have clear zones about them. A cresyl blue stain colors the outer surface of these organisms and shows that even the smallest has a thin membrane or wall. With hematoxylin the wall of the small forms scarcely stains, so that one sees principally the chromatic material, and an impression is gained of extreme minuteness. In the spaces the organisms frequently occur as one large organism, and many small ones, the latter frequently about the periphery of the space. In spite of the enormous numbers of small organisms in contrast to the fewer larger ones, no evidence of a process of endosporulation is found. The only suggestion of it is the finding once of a large cell with many small chromatin masses of varying size irregularly distributed in the cell. Frequently the larger organisms are seen giving off the minute forms as buds.

The reaction in the lung is very slight, and consists of a perivascular exudate of plasma and lymphoid cells, with production of large mononuclear and giant cells containing organisms. Occasional small hemorrhages are seen. In some areas there is a formation of dense connective tissue about the organisms, forming nodular masses, infiltrated slightly with lymphoid and plasma cells. Other sections show areas of diffuse production of connective tissue.

Spleen.—A lesion extends into the pulp from the surface. It consists of a formation of dense connective tissue with a loose meshed tissue on the peritoneal side enclosing spaces filled with organisms. The organisms are nearly all of the large resting cell type. They show signs of degeneration, and reproduction is not active. In another place there is a formation of dense connective tissue on the peritoneal surface of the spleen with a number of mononuclear eosinophilic cells and a few barely recognizable organisms.

Kidneys.—A number of small irregular areas of dense connective tissue contain a few thick walled organisms. Sometimes an area encloses an atrophic glomerulus. One area of dense connective tissue extends in irregularly from the surface. Honeycombed spaces in the center contain hyaline organisms. In one place dilated tubules with atrophic epithelium contain organisms, and nearby tubules on close examination show small organisms in the epithelium, causing its destruction. About the infected areas are a few lymphoid and plasma cells.

Liver.—A lesion extends in from the surface, consisting of a caseous center containing large organisms, then a layer of giant cells and epithelioid cells containing organisms, beyond which is a thick wall of connective tissue.

Brain.—A chronic meningitis is found in all sections, varying somewhat from a slight cellular infiltration to a marked thickening. Large numbers of small and fewer large organisms are present everywhere. The cell reaction consists of lymphoid and plasma cells, and a few giant cells, but principally of large phagocytic mononuclear cells. Rare polynuclear cells occur. Connective tissue formation is beginning.

The organisms always occur with clear zones about them, demonstrated by special stains to consist of a gelatinous material. There are extensions into the cortex forming lesions with solution of tissue filled with gelatinous material, and absence of reaction, exactly like the peculiar brain lesions in the first case. The only difference is in the great number of small organisms present in the large phagocytic mononuclear cells which have invaded the lesion. The small organisms are seen in the substance of the cortex and the edge of the lesion, causing its disintegration. In some of the lesions there is considerable production of large phagocytic mononuclear cells which are filled with the small organisms; in other lesions these cells are few. Cresyl blue stains the gelatinous material in the lesions as in the first case. There are several lesions in the cerebral cortex, and in the cerebellum.

The small organisms occurring in large numbers are in contrast to the lesions of the case described by Frothingham, from which the organism was obtained. Evidently, as in the coccidioidal disease, where enormous numbers of sporulating forms were found in the lesions in mice, the small animals furnish a particularly favorable ground for their multiplication.

Rat 2.—Inoculated Apr. 25, 1915, by an injection of 1 cc. of a salt solution suspension of torula into the right pleural cavity; killed May 15. No external lesions. The peritoneal cavity appears normal. A smear shows no organisms, and cultures give no growth. Small white spots, 1 to 2 mm. in diameter, are found in the liver and kidneys. The spleen and lymph nodes appear normal. Both lungs are filled with gray nodules about 1 mm. in diameter. The brain appears normal externally.

Microscopical Examination. Lung.—Scattered throughout sections of the lung are miliary nodules which often occur in groups of two to ten, like miliary tubercles, the adjacent nodules often coalescing to form larger ones; these are composed of collections of epithelioid cells with a few lymphocytes and occasional giant cells. About the periphery of the nodule there is slight connective tissue formation, and there are often numbers of eosinophilic cells. The alveoli next to the nodules appear normal. In some of the nodules torula organisms can be found. They occur in the center, often with a few eosinophilic cells, and show all stages of degeneration to complete destruction. The majority of the nodules contain no intact organisms; in some not even remains of organisms can be made out. These nodules are indistinguishable from miliary tubercles, produced by the tubercle bacillus, except for the presence of the organisms. In some cases there is a slight central caseation, but usually none is present. Giant cells vary much in numbers; sometimes six or seven occur in a section of a nodule, in others there are none. Although they often contain the organisms, their number does not seem to be in relation to the numbers of the torulæ.

Spleen.—Tubercles similar to those in the lung, but of larger size and with central caseation, are found. In some nodules remains of the small forms of the torulæ but no large forms can be seen.

Peritoneal Nodule.—There is a diffuse chronic inflammatory tissue very much like that of the meninges with lymphoid, plasma, and epithelioid cells. Eosinophilic cells are scarce as a rule, but are often numerous about vessels. Giant cells occur diffusely; a few organisms, in a partially disintegrated condition, are seen.

There are large and small coalescent areas of necrosis with partial caseation in which torulæ are numerous. The caseous material is partially honeycombed with spaces, in the centers of each of which one of the larger forms of the torulæ is seen. Remains of cells can often be seen in the caseation, and fibrin is often present at its periphery.

The whole picture is similar to an advance tuberculous node, except that the caseation is not complete and there are often visible torula organisms.

Kidney.—Miliary collections of epithelioid and giant cells as in the lung.

Liver.—Perivascular collections of lymphoid, plasma, and many eosinophilic cells, and a few miliary nodules similar to those described above.

Brain.—A chronic meningitis in some of the large sulci with extension into the cortex. The whole picture is just like that in the rat previously described, except that the organisms are undergoing greater destruction and the lesion is being invaded by the chronic inflammatory tissue from the meninges. This shows the chronic recoverable character of the brain lesions caused by the torulæ.

Rat 3.—Inoculated Apr. 25, 1915, by an injection of 1 cc. of a salt solution suspension into the heart. The culture was obtained from the peritoneal cavity of Rat 1. On May 15 the animal was noted to be sluggish in reaction and to keep in a crouching position with somewhat labored breathing. Gradually the symptoms became more marked and finally the animal no longer attempted to defend itself when touched, and when rolled over righted itself with difficulty, and walked slowly with a dragging gait. The hind legs seemed weak, and the animal could not run.

On May 25, 4 weeks after inoculation, the animal was chloroformed and autopsied. The peritoneal cavity appears normal. Many small gray nodules are found in the kidney, from 0.33 to 1 mm. in diameter. A few very small gray nodules in the spleen appear to be different from the Malpighian bodies. No lesions in the liver. The retroperitoneal nodes appear normal. The lungs are a little more firm than normally, and contain many nodules similar to those in the kidney. In the mediastinum is a thickened fibrous mass of tissue in which enlarged lymph nodes are found containing miliary lesions. The brain is considered to have a few minute nodules, but their presence is not certain.

Cultures on potato and dextrose agar from the meninges, and from the lung and kidney lesions give pure growth of torula.

Microscopical Examination. Brain.—In five sections from five different blocks of the cerebrum and cerebellum forty-two lesions are found in the brain substance, and many areas of infection of the meninges. The lesions in the brain are perivascular or extensions from the meninges. They are all in a stage of healing, and show a high degree of destruction of the parasites. Sometimes in a lesion are only one or two large collapsed organisms, or there may be a small collection of the large non-granular spheres. The small forms so conspicuous in the rat that died from the injection are almost entirely absent. The method of extension of the brain lesions by a solution of the tissue by the individual organisms is plain. The reaction in all is of an extremely chronic character. There are accumulations of plasma and lymphoid cells with a few large mononuclear cells in the perivascular lesions. Almost all the reactive cells in the lesions with solution of tissue are the large mononuclear cells, probably glial in origin. The meningeal reaction is similar to the perivascular. Many lesions are present in the cerebellum, especially in the cortex. There is a distinct production of thick glia fibers in the outer layer of the cerebral cortex. The whole picture here is strikingly similar to our first case. A lesion is found in the choroid plexus of the third ventricle consisting of an ill defined accumulation of mononuclear cells. The choroid plexus of the fourth ventricle contains an almost perfect imitation of a miliary tubercle, without caseation.

Kidneys.—Numerous single and conglomerate tubercles are present, some with a few hyaline or collapsed large torula forms, others in which none can be made out. In several instances large thick walled organisms are seen in glomeruli. The character of the tubercles is the same as in Rat 2. There is occasional necrosis in the center, with remains of organisms, the material staining a nearly uniform pink and resembling caseation. Occasionally there is a diffuse infiltration with lymphoid cells between the tubules.

Liver.—Many small lesions are seen, consisting of collections of lymphoid cells about small masses of hyaline organisms in the periportal tissue. Sometimes dense connective tissue in considerable degree is formed.

Spleen.—Frequently in a large giant cell eccentrically placed in a Malpighian nodule are numbers of small torulæ.

Lungs.—Numerous miliary nodules as in Rat 2. More often recognizable organisms can be seen.

Lymph Nodes.—(Mediastinal.) Numerous and large lesions like those in the peritoneum in the preceding case. The reaction is almost entirely of epithelioid and giant cells with formation of connective tissue. Often a ring of connective tissue encircles the clear zone about an organism. There are also miliary lesions like those previously described. Some of the lymph sinuses are distended with organisms which have not yet excited a reaction.

Stains for tubercle bacilli were made, but no organisms found in any of the tubercles.

Rats 4 and 5.—Inoculated intraperitoneally on Apr. 25, 1915, with a few drops of a thin salt solution suspension of torula from the original culture. 2 weeks later inoculated intraperitoneally with 2 cc. of a thick suspension of torula obtained from Rat 1. No symptoms of illness. Killed May 25.

No lesions in gross except in the retroperitoneal lymph nodes, which are enlarged, with miliary white areas, and in the peritoneum covering the spleen and kidneys.

Cultures from the peritoneal cavity, heart's blood, and brain give no growth.

Microscopical Examination.—The absence of lesions in the organs is confirmed. The lesions in the retroperitoneal nodes are extensive and of the type already described.

Rats 6 to 18.—Inoculated intracardially on June 22 with 2 cc. of a salt solution suspension of torula recovered from Rat 1. Rat 6 died on the 2nd day, Rats 7 to 10 on the 5th day, Rat 11 on the 6th day, Rats 12 to 14 on the 7th day, Rat 15 on the 9th day, Rat 16 on the 10th day, Rat 17 on the 11th, and Rat 18 on the 12th day. Symptoms of illness consisting in lack of vigor and alertness preceded death by 1 to 2 days. At autopsy pneumonia and pleurisy of the type already described were found in all the rats except Nos. 6 and 9. In gross the only other lesions noted were enlargement of the spleen and lymph nodes.

Pure cultures of torula were recovered from the spleen and liver of Rat 6, from the spleen of Rat 12, and from the spleen and meninges of all the other rats.

Microscopical Examination.—Brain lesions are seen in every case, besides miliary lesions in other organs, which are sometimes extensive. The type of reaction is that previously described. In no case can an acute exudate be found. In the brain lesions reaction is practically completely lacking, even though a considerable amount of reactive tissue exists in the other organs. The brain lesions are smaller than in the rats killed later, while the lesions in the other organs are, as a rule, more extensive. Apparently the torula grows faster, but excites more resistance in most organs, while in the brain it grows slowly but keeps on for a longer time.

Control Examination.—Six uninoculated rats from the same lot were autopsied and examined histologically to be sure that similar diseases did not occur spontaneously in the animals. No lesions were found.

7. *Agglutination Experiments.*

Agglutination tests were done on sera taken from all the inoculated animals. In the first series blood was taken from the heart on Jan. 17, and the sera were kept in the refrigerator. On Jan. 18 a suspension of the torula organism was tested against the sera in dilutions of 1:20, 1:100, and 1:1,500. The tubes were put in the incubator and readings made in ½ hour and 2½ hours; the tubes were then kept at room temperature, and a third reading was made at the end of 12 hours. All tubes showed the same degree of clearing, with sediment of similar appearance. On Jan. 19 a torula suspension was tested against the sera again in dilutions of 1:2, 1:10, 1:1,000, and 1:5,000, and readings were made as before. All tests were negative.

On Jan. 22 oidiomycosis and coccidioidal organisms were similarly tested with all the sera, and no agglutination was found in dilutions of 1:2, 1:20, 1:100, and 1:500.

All tests were then repeated in dilutions of 1:2, 1:20, 1:100, and 1:500, and found negative. In all tests salt solution and sera of normal rabbits and pigs were used as controls.

Of the animals tested, four were found at later autopsy to have lesions produced by the torula; one rabbit, one dog, one guinea pig, and one mouse. Of the animals inoculated with oidia, none had lesions. Five animals had coccidioidal lesions,—three guinea pigs, two rabbits, and a mouse.

In the second series macroscopic and microscopic agglutination tests were done on the sera of the mice and rats infected with torula and oidiomycosis. The rats infected with torula proved later to have extensive lesions. First a suspension of the torula was tested against the sera of two mice infected with torula and one rat infected with oidiomycosis in dilutions of 1:20, 1:30, 1:90, 1:180, 1:540, and 1:620. The readings were made as before. No definite agglutination could be made out.

The microscopic tests were made in dilutions of 1:10, 1:30, 1:90, 1:180, 1:360, and 1:720, and were examined at intervals for 18 hours. No agglutination occurred. The microscopic tests were repeated with negative results.

Later it occurred to us that possibly the gelatinous secretion of the torula interfered with the physical conditions necessary for the test, as in the case of Friedländer's bacillus and other encapsulated bacilli. Consequently treatment with acid, according to the method of Porges and Prantschoff, was tried. Dilutions were made of 1:2, 1:50, 1:100, 1:200, and 1:500. After 2 hours in the incubator complete agglutination was found in the sera of one mouse in dilution of 1:50, partial in dilution of 1:100, a questionable slight clumping in dilution of 1:150, and none in 1:200. This test occurred in a mouse which was autopsied at the time blood was taken and found to have a sticky peritoneal exudate from which a pure culture of torula was obtained. The test was made about 3 weeks after inoculation. The other mouse gave slighter agglutination. This mouse had been inoculated only 3 days previously, but at autopsy at the time of the experiments had a peritoneal exudate containing a pure culture of torula. Careful control tests with normal rat blood, however, showed practically the same degree of agglutination. The tests were also carried out by this last technique on the blood of Rats 3, 4, and 5, taken at the time of autopsy, and the same results obtained.

Conclusion.—No agglutination test of diagnostic value occurs in an infected animal.

8. Cultural Characteristics of Torula.

We repeated and confirmed the observations previously reported in regard to Frothingham's torula. Observations were made on cultures growing under varying conditions of temperature and moisture on many media. Direct observations of growth were made on agar slides and in hanging drops. Reproduction was always by budding. In cultures fresh from animals the production of small forms about 1.25μ in diameter occurred.

Fermentation tests in 1 per cent lactose, saccharose, dextrose, dextrin, and glucose, in Smith fermentation tubes, resulted in no gas production.

No spore production was found in cultures or in our observations of growth on gypsum blocks. Extensive observations of gypsum cultures had already been made by Weis.

The growth at first was most abundant on carbohydrate media,—potato and agar or dextrose agar,—and was extremely scanty on blood serum. After animal inoculation growth occurred more vigorously on blood serum, but never so abundantly as on the dextrose agar or potato tubes. No growth or very slight growth occurred in anaerobic cultures. Growth first occurred in 12 hours to 4 days. It was nearly as vigorous at room temperature as in the incubator. The colonies are first white, then they acquire more and more of a yellow tinge as they grow older. Colonies starting from a single organism become much heaped up, probably from the adhesive nature of the capsule. In the usual tube inoculation a smooth, pasty, slightly shiny, thick, slightly yellow layer is formed. No liquefaction of media or growth into media or along stabs occurred. In bouillon, after a week, there is slight cloudiness, but no surface growth. Most of the growth in liquid media occurs as a fine white deposit at the bottom of the tube. In bouillon cultures a white growth along the glass above the surface of the media occurs in about a week.

Microscopical Examination.—The cultures show round cells from 1 to 6μ in diameter, the average size being 3 to 4μ.

Buds form from large cells or from the smaller cells, but most often from the medium sized cells. The buds measure usually about 1 to 1.5μ in diameter. They may attain a diameter of 2.5μ before separation. Sometimes the bud reaches nearly the diameter of the parent cell.

As the bud begins to separate a deposit of gelatinous substance forms about the neck of the bud, and after separation occurs it appears as a thick line at the area of separation. The substance stains blue with methylene blue, a dark purple with Wright's stain, and a red color with Giemsa's stain or fuchsin. When cells occur in masses, this substance forms similar lines between adjacent cells, and the cells often are flattened to form hexagons. If the cells become separated the material is drawn out into fine threads connecting the cells, similar to those in the cases. The torula tends to occur in masses in cultures, probably on account of this secretion. When growing in hanging drops it forms close groups.

The medium sized torula cell has a definite wall 0.5 to 1μ thick, staining easily with methylene blue or with Gram's stain. The cell interior, as a rule, cannot be made out to have a definite nucleus. Examination of the organism from cultures is much less satisfactory than in sections of animal lesions. In smears from young cultures a stain with methylene blue shows one to six small, very dark staining masses, irregularly distributed in the cell. In old organisms these are not present. The whole interior of the cells in young cultures usually takes a deep blue stain, in which one or more lighter staining areas may be apparent. Rarely the interior appears coarsely granular. In older cultures, especially in the larger cells, the interior does not stain so uniformly. There is a darker staining mass in a light staining cell. The mass sometimes appears like a nucleus, and occasionally is surrounded by a thin line like a membrane and may contain a vacuole. In some cases the vacuole appears to have distended the mass, so that the dark staining material lies next to the cell wall. Similar appearances are seen in the animal lesions. With Wright's stain a definite darker staining mass one-third to one-half the diameter of the cell is usually present, eccentrically situated, in the smallest organisms. In the larger ones the mass becomes more irregular in outline and position. In the process of budding part of the chromatic material flows out into the bud and is separated by the constriction of the bud. No nucleolus can be made out.

Torulæ are widely distributed in nature. They occur in the earth, on trees and fruits, in wasps' and bees' nests, and on these insects. Classification of different varieties has been attempted, but is unsatisfactory, on account of the slight and inconstant differences. Weis, in an investigation of four torulæ, found great similarity. None of them fermented sugars. The principal differences were as to the presence or absence of close or open budding, whether they formed top or bottom growth in liquid media, the presence of growth on the glass of the tube, and the amount of gelatinous secretion. These characteristics varied greatly until the organisms had been under cultivation for months. Our torula shows close budding, bottom growth with no growth on the surface, yeast ring after a week's growth, and distinct gelatinous secretion.

VI. TABLE OF DIFFERENTIAL POINTS BETWEEN TORULA INFECTION, OIDIOMYCOSIS, AND COCCIDIOIDAL GRANULOMA.

Torula infection.	Oidiomycosis (usually termed blastomycosis).	Coccidioidal granuloma.
	Cell wall.	
Stains diffusely and easily with methylene blue and hematoxylin.	Does not stain, as a rule, with methylene blue or hematoxylin. Occasionally in deeply stained preparations it partially takes a faint color.	Stains faintly with hematoxylin and methylene blue, but not diffusely; the inner and outer layers are principally stained.

TABLE OF DIFFERENTIAL POINTS—*Continued.*

Torula infection.	Oidiomycosis (usually termed blastomycosis).	Coccidioidal granuloma.
Protoplasm.		
In large forms not evident. In medium sized forms often shrunken into an irregular shape, and takes a diffuse red stain with few differentiated droplets. In small forms fills the organism and has dark staining masses.	Usually slightly shrunken regularly from the wall. Usually stains well and appears uniformly granular, with occasional vacuoles or droplets. It colors a reddish blue with eosin and methylene blue.	Adheres to the capsule, often forming a rim inside it. It is greatly variegated with all the changes attendant on the process of endosporulation. Stains well as a rule.
Size.		
1 to 13μ.	3 to 4μ to 20μ.	5 to 85μ.
Reproduction.		
By budding, often with the production of small organisms which can bud before enlarging.	By budding; usually the bud is ½ to ⅔ the diameter of the parent cell and grows to the original size before it reproduces.	Never buds. (Buds may be simulated by cells in apposition.) Produces ascospores.
Occurrence.		
Always with a clear zone about it composed of gelatinous material.	No clear zone except in rare cases in the bone marrow.	No clear zone.
Cell products.		
A gelatinous material which often fills the lesion.	No gelatinous material.	No gelatinous material.
Action on tissues.		
Destroys the cells it is enclosed in and appears in large vacuoles which are probably due to destruction of the cell protoplasm.	Distends the cells it is enclosed in, but does not occur in large vacuoles.	Distends the cells it is enclosed in, is closely surrounded by the cell protoplasm, and often the cell shows no evidence of injury.

TABLE OF DIFFERENTIAL POINTS—*Continued.*

Torula infection.	Oidiomycosis (usually termed blastomycosis).	Coccidioidal granuloma.
Character of lesions.		
1. Lesions with solution of tissue, filling with gelatinous material, slight chronic reaction.	No such lesions.	No such lesions.
2. Nodules with or without caseation composed of epithelioid cells, giant cells, and lymphoid cells. Caseation occurs centrally and apparently depends on the action of the cell products.	Nodules with or without caseation. Caseation is secondary to a crowding of cells, apparently.	Nodules composed of epithelioid cells with occasional giant cells. Caseation is secondary to large accumulations of cells and is peripheral.
No collections of polynuclear cells.	Abscesses deep and superficial.	Abscesses deep and superficial.
No cutaneous lesions.	Miliary epidermoid abscesses.	Cutaneous ulcerations.
Does not attract polynuclear leukocytes in any stage.	Usually attracts polynuclear leukocytes.	The smaller forms especially attract polynuclear leukocytes.
Clinical course in man.		
A chronic disease of the nervous system, without constant or great fever or leukocytosis.	A chronic skin disease or general infection with fever and leukocytosis.	A chronic skin disease or a general or brain infection with fever and leukocytosis.
Organs affected.		
Brain and meninges, lungs, liver, spleen, kidneys. Not skin or bones.	All organs, always the skin, often the bones.	All organs, often the skin.
Reaction to treatment.		
Not helped by salvarsan. No data as to effect of iodides.	Usually helped by iodides.	Not helped by iodides.

TABLE OF DIFFERENTIAL POINTS—*Concluded.*

Torula infection.	Oidiomycosis (usually termed blastomycosis).	Coccidioidal granuloma.
	Pathogenicity in animals.	
Marked for mice and rats, slight for guinea pigs, rabbits, and dogs, where brain lesions are the principal ones.	Slight or absent for all animals tried.	Marked for all animals tried.
	Organs affected in intraperitoneal inoculation.	
Brain, lungs, liver, spleen, kidneys.	Peritoneum, occasionally lungs. Experiments reported in which miliary abscesses or nodules were produced in various organs by intravenous inoculation. None mentioned in the brain.	Lungs, spleen, liver, kidneys, peritoneum.
	Organism in culture.	
Reproduces by budding. Never produces mycelium.	Always grows mycelium sooner or later.	Always grows mycelium and aerial hyphæ.

VII. DISCUSSION.

Historically there is great interest in the fact that torulæ were proved years ago by several observers to have marked pathogenic action in animals, with frequent production of brain lesions. It was also shown that torulæ are widespread organisms in nature. It would not have been too venturesome to have prophesied that the organisms would be found at some future date producing nervous disease in man. We have found that cases do occur. It will take time to determine how common this type of infection is, but many facts indicate the possibility of its being frequently present without recognition. A number of factors work to conceal its nature. The organism is not very pathogenic and the lesions are recoverable. Thus, many infections may occur during life without causing noticeable symptoms. At autopsy lesions may be found, but, if in the healed stage, the organisms will be practically or absolutely indistinguishable, and the picture that of a slightly atypical tuberculosis, caseation being slight or absent. In animals we frequently produced lesions in nearly all organs, some of which were indistinguishable from miliary tubercles without caseation, or with slight central necrosis. In our human cases the slight lesions outside of the nervous system produced no symptoms in the first case; in the second case, with extensive lung lesions, only an indefinite history of lung symptoms is given. The lesions closely resembled tuberculosis, and in them the organisms had practically disappeared. Without brain examination we could not have recognized the nature of the cases. In the literature are many cases of nodular lesions in internal organs which do not seem to be tuberculous in origin, although the lesions resemble tubercles. Wolbach reports several, and mentions peculiar crystalloid bodies in the giant cells, which we found in our second case. Other cases in our recent hospital records are of the same character. Thus the tendency toward recovery, the often slight involvement of organs, the destruction of the parasite, and the resemblance to tuberculosis, render it possible that the infection is common, but not recognized.

The probability of its recognition in brain examinations is greater, but even here there are several sources of error. The gliosis and thickened meninges, with slight atrophy of the convolutions, the chronic character of the meningitis, with many plasma cells, and often hyaline organisms, make confusion with syphilis easy. When the lesions have progressed to caseation, the diagnosis of tuberculosis might be made. There is no identity on careful examination; the caseation is not typical, its character and distribution are different, and only careful microscopical examination shows the organisms. The perivascular lesions are often small and would escape discovery unless the brain were completely sectioned. Many cases would easily escape recognition in the often careless routine brain examination.

The factors which will aid the recognition of torula infection are: discovery of early lesions in internal organs before the parasite is destroyed; realization of the finer points of difference from tuberculosis; complete brain examination; cultures, especially on carbohydrate media at room temperature; and injections of fluids and cultures into white rats intraperitoneally, with microscopical examination, especially of the brain.

Torula infection is essentially a chronic disease. In man the symptoms are measured by months; in animals the lesions last weeks or months. Its total duration as a general disease cannot be determined in the human cases, for the first organ lesions probably produce no symptoms. As a nervous disease it is clinically essentially chronic, and the pathological reaction is always one of extreme chronicity.

The lesions in internal organs, outside of the nervous system, are recoverable. In the human cases and in nearly all the animal cases there is evident a strong tendency toward destruction of the parasites, with the production of small nodules or large masses of connective tissue. In our animal experiments we have seen the various stages of this conversion. In one animal, however, which died from the infection after 5 weeks, there was no tendency toward recovery in the lung lesion, but some in the other lesions. Rusk's case and Frothingham's case showed similar lung lesions. In the brain the tendency toward recovery is not so marked. Many of the lesions in the human and animal cases, especially the intracerebral lesions, show little evidence of defense by cell proliferation or destruction of the organisms. In other instances there is marked phagocytosis by invading mononuclear cells with partial disappearance of the organisms; and in some animals all the brain lesions are seen in a healing stage. The meninges have a more effective defense than the brain.

As to localization of lesions and organ resistance, the animal experiments show a marked tendency to the production of a general infection from intraperitoneal inoculations, with especial involvement of the nervous system. Lesions were found in the brain, meninges, lungs, spleen, liver, kidneys, and lymph nodes. The liver showed the least extensive lesions, the spleen more involvement, and the lung, kidney, and brain the greatest involvement. Sometimes there was more involvement of the brain than of any other organ. This was the case especially in the higher animals. In the dog there was only one small lesion in the kidney; there were none in the other organs, but many small nodules in the brain. The rabbit had one liver lesion, but no other lesion except a meningitis of considerable extent. The mouse inoculated intraperitoneally with the ventricular fluid had only a meningeal lesion; a mouse inoculated with the torula culture had only a peritoneal lesion, besides the meningitis. In all rats there was a general involvement of many organs, but the brain lesions in the later stages showed more evidence of activity than those of other organs. The same distribution is evident in the human cases; in our cases the organ lesions, as a rule, were insignificant with the exception of the lung lesions of the second case. Histological examination shows a greater destruction of the organisms in the spleen, kidney, and liver than in the lung, and in the lung greater than in the brain. The brain, however, has some power of resistance and recovery. The results all show the peculiar low resistance of the nervous system to torula infection. In higher animals where the resistance is more marked the difference between the lesions in and outside of the nervous system becomes more striking, for here the nervous lesions are the only ones which form or progress in any degree.

The tendency toward the production of brain lesions is in sharp contrast to the action of the other organisms studied, where intraperitoneal inoculation produced brain lesions in no case. Our experiments again support the differences in the human cases, and show that organ resistance in man is not different from that in animals.

The localization of the lesions in the nervous system is in the meninges, in the perivascular spaces, and in the brain substance by extension from these lesions. In the human cases and in animal experiments lesions were also found in the choroid plexus, in one human case in the aqueduct of Sylvius, and in another about the foramen of Magendie. Lesions in the basal ganglia, internal capsule, frontal lobes, and cerebellum occurred. A perineuritis was seen in one case. This tendency toward localization in critical points obviously makes the production of even small lesions of great importance. In animals the same distribution is evident, involvement of the cerebellum being especially noticeable.

Resulting from the chronicity and localization of the lesions are the symptoms in man. Fever was evident only at the onset in the cases and was moderate in degree, the white count was low in one case when fever was present and in others at various periods. We have already discussed the spinal fluid findings in the cases. The variability of the localization will evidently cause no constant symptomatology. The tendency to involve the cerebrospinal fluid pathways is of extreme importance as a method of production of internal hydrocephalus which will cause confusion with cerebral tumor, especially in connection with the localizing symptoms of the other lesions. The optic nerve may become involved, or choked disc may be secondary to other lesions. The frequent occurrence of psychic symptoms is in accord with the tendency toward involvement of the frontal lobes and basal ganglia.

With the exception of syphilis there is little accurate knowledge of recoverable chronic infections of the central nervous system. There is clinical evidence in the reports of pseudotumors and other conditions that such cases may not be uncommon, and the torula infection may have importance in this regard.

The Mechanism of the Disease.—The mode of infection in the human cases is uncertain. Of especial interest is the lesion in the esophagus in Türck's case, from which organisms were isolated similar to those in the spinal fluid. However, yeast-like organisms are common in the throat, and a similarity in cultures cannot be taken to mean identity. In our second case a sticky pharyngeal exudate was noted, but no examination made. In Rusk's case and in our second case there was an evident possibility of origin in an infection of the lung. On the whole, the respiratory tract, as in oidiomycosis, seems the most probable atrium. It is possible that infection may occur together with a tubercular infection. Ascending infection through the fallopian tubes is a possibility.

The path of distribution after infection occurs, in many cases at least, is through the lymphatics to the blood stream. Our second case, with the numerous lesions in the bronchial lymph nodes and the miliary lesions in the spleen and liver, suggests this mode of spread. In the animal experiments transport by lymphatics is plain. Lesions in the retroperitoneal nodes after intraperitoneal inoculation were marked. In an intrathoracic injection, mediastinal nodes were involved. The miliary lesions in all organs are due to blood infection.

In all lesions engulfment of organisms by giant and large mononuclear cells was a marked feature. The organisms continue to live and multiply within these cells and after destroying them are set free. Thus the methods of defense on the part of the host may spread the infection.

In the brain lesions additional methods of spreading are evident. Organisms are carried along the perivascular spaces of the vessels and start new intracerebral lesions. Or there is direct extension by solution of tissue. This extension by methods similar to those of the ameba is not so evident in other organs, probably because the resistance is so much greater that the organisms are quickly destroyed. It did occur, however, in the lung of an animal with low resistance. Nerve lesions are started by organisms carried into the sheath by the fluid currents.

In the study of the relationship of the organism to its host histology furnishes evidence of a method of attack by mechanical means, the pressure of the growing mass of parasites, and by chemical means, the destruction of the cells of the tissues. The latter factor is the more important. Another means of offense is a weakening of the host by the accumulation of its defensive cells in critical spots so as to interfere with function. In this mode of attack the torula has the great advantage of being able to produce lesions easily in the nervous system, and in almost any part of the nervous system. In our cases it was evident that a great deal of the disease picture was produced by the interference with the passage of cerebrospinal fluid by focal lesions; and the weakening of the host produced by the internal hydrocephalus gave the organism a chance to multiply with greater freedom.

In the older lesions the organism becomes fainter staining, or collapsed, and finally disappears. In some cases only miliary lesions exist. Old cultures of torula do not show disappearance of the organisms, so that the destruction in the lesions is probably by the action of the tissues. The destruction occurs in cells or out of cells. In some cases, however, it is not evident. No production of agglutinins was found in any case. A further advantage possessed by the torula is the production of the large thick walled resting cells. These are typical of torulæ in nature, which are highly resistant and long enduring. Dried up cultures of torula several years old immediately grow with rapidity when transplanted, and are pathogenic. In one rat the histological study of the meninges showed only the large, almost hyaline forms, but a pure culture was obtained with ease. It is probable that the infection can remain dormant for a long time, and then start up afresh. We have direct evidence of this in our second case, where the lung, lymph node, and liver lesions were old, the lung lesions consisting of hyaline connective tissue masses, with only a few thick walled forms, while the brain showed a very active process with young forms predominant. The cerebellar lesion in our first case was an old lesion, consisting almost entirely of the resting cell forms. Here the struggle between the parasite and the tissues had apparently come to a standstill.

The Mode of Multiplication of the Organism.—The small, actively budding organisms found under favorable conditions of nutrition, and the resistant spheres under unfavorable circumstances adapt the parasite to most various conditions.

The histology of the lesions has been fully described, but the relationship of the two principal types has not been explained. The experiments give a plain solution of the question, and show part of the mechanism of the lesions. Possibly the lesion starts by the passage of a small torula into the tissue while in a phagocytic cell from the blood stream. It multiplies within the cell and destroys the cell, and then the organisms are liberated. A single organism in an endothelial cell or a few small organisms in a giant cell have been found as the early lesions. The organism then multiplies and produces a gelatinous material which surrounds it. Phagocytic mononuclear cells gather and take up organisms, which multiply within them, destroy the cell, and are set free. Giant cells form and undergo a similar process. The surrounding tissue meanwhile is partly pushed apart, partly dissolved. Strands of connective tissue often form about the gelatinous capsule, giving rise to a honeycombed appearance, the spaces each containing an organism. This is a stage common to all types of lesion. The varying degrees of resistance of the animal determine the further fate of the lesion. In a non-resistant animal or organ, the ameba-like extension by solution of tissue occurs, with a feeble defense by the production of mononuclear cells and slight connective tissue. This type of lesion occurs especially in the brain substance, but is seen in the lung and to a less extent in other organs. It is a striking and characteristic lesion.

If the animal is comparatively resistant, there is more cell accumulation and proliferation, with some destruction of the organisms. Epithelioid and lymphoid cells gather, the central part of the lesion undergoes necrosis and partial caseation, in which at first the organisms can be seen in honeycombed material, and later almost disappear. In lymph nodes this type of lesion is most extensive and furnishes a resemblance to a scrofulous gland. If the destruction occurs promptly the lesion is small and nodular, with slight central necrosis or caseation or none, and is like a miliary tubercle. Organisms may or may not be recognizable. Lesions thus were found in all organs. If infection occurs simultaneously, in many adjoining foci, there is a diffuse chronic inflammatory tissue consisting of giant cells, lymphoid, epithelial, endothelial, and plasma cells, with connective tissue formation, and torulæ enclosed in small spaces. Such lesions are especially frequent in the meninges and correspond to diffuse tuberculous tissue. Early and slight diffuse lesions in the meninges and brain call out only fluid and large phagocytic mononuclear cells. When the organisms are overcome quickly, there is slight production of gelatinous material, but gelatinous encapsulation is always plain. Very old lesions become converted into fibrous tissue masses.

On account of the histolytic action so striking and characteristic in early lesions and in brain lesions, it is suggested that the organism be called *Torula histolytica*.

We wish to emphasize the fact that not only do the lesions resemble those of tuberculosis, but they resemble them more closely than do the lesions of any other disease. Coccidioidal granuloma, considered by some authors to produce lesions indistinguishable from tuberculosis, in our experiments showed a marked tendency toward miliary or larger accumulations of polymorphonuclear leukocytes, especially around sporulating organisms. Caseation was at the periphery of large collections of polynuclear and epithelioid cells and did not occur in the small epithelioid cell masses. The parasites were large and easily seen. Oidiomycosis bears still less resemblance to tuberculosis. In torula infection the parasites are often hyalinized and, being about the size of tissue cells, are almost impossible of recognition in advanced lesions.

VIII. SUMMARY.

One of the problems in our work was the relationship of the organisms causing the diseases termed blastomycoses. We have shown the confusion existing in text-books, where the various diseases are described as one disease, or as different manifestations of the action of a single organism in different states. The study of the literature convinced us that coccidioidal granuloma was a disease distinct clinically, pathologically, and biologically from other diseases called blastomycosis. The work of Wolbach, and MacNeal and Taylor, who described the life cycle of the organism of dermatitis coccidioides, never present in the other cases, makes the biological distinction evident; the summaries of Ophüls, Ryfkogel, Hektoen, and Brown and Cummins, establish the clinical differences. We have not regarded it necessary to repeat these summaries. Our experiments bear out the former work. The lesions produced by *Coccidioides immitis* are not to be easily confused with those of blastomycosis, or torula infection. For the details of the differences between the diseases we refer to the discussion in the review of literature and to the table. We lay emphasis on the point, not because we do not consider that other workers have not made it sufficiently clear, but because it is not yet recognized in text-books, and because our experiments bear out the former statements.

Having seen that coccidioidal granuloma was a distinct disease, we turned our attention to the blastomycoses. We found in the literature two cases of skin and general infection produced by a true yeast, with endospores in culture. Both cases were observed by Buschke, and appeared to be distinct from the American cutaneous disease. Frothingham's discovery of torula infection in a horse indicated another type, but no such cases had been reported in human beings.

Our cases were distinct from the larger part of the reported cases of blastomycosis in their clinical histories and pathology. It did not seem improbable that in the early study of blastomycosis such cases had been described, but their nature not recognized. We studied the original reports of all the cases of systemic blastomycosis and found that nearly all the cases were similar to each other as far as we could tell from the printed reports, except those involving the brain. Among these there were obvious differences. First there were six cases like the other systemic cases, but in which the brain became involved as part of the general infection, which always included skin manifestations and often bone lesions. The symptomatology was not perceptibly influenced by the brain lesions. The pathology of the brain lesions resembled that of the other lesions. Different from these were four cases in which there were no skin lesions, but in which a general infection occurred with brain lesions which caused the predominating symptoms. Pathologically the lesions were distinct in many ways; but principally in the extension by solution of tissue, the always chronic reaction, and the production of a gelatinous material in the lesions.

Our first case was evidently identical with this latter group. Our second case was not fully identifiable by the study of the literature alone, for the peculiar intracerebral lesions were not present, and the parasite occurred in greater numbers of small forms. Such forms occurred in the meninges of the first case, but not in the intracerebral lesions, and were not described in the literature. In the experimental meningitis in a mouse produced by the injection of a culture of the ventricular fluid from the second case, however, large organisms were produced, identical with those of the first case, and intracerebral lesions of the same type were seen in process of formation. Thus our two cases were proved to be alike in origin.

Frothingham's case of torula infection was evidently the type of infection of these cases. In our animal experiments with torula we found both forms of parasites present in the lesions in varying proportions according to the extent and activity of the process. In a very active lesion enormous numbers of small organisms similar to those of the second case occurred; these were seen especially in the meningeal lesions. In older lesions, tending toward recovery, or in those slowly progressing, and in the higher animals, the larger forms predominated. In sections of the original horse lesions, small forms are entirely absent. Our experiments resulted in the production of all the variations in lesions and organisms seen in the cases. The animal experiments thus provided the necessary steps for the clear correlation of all the human cases as cases of torula infection.[1]

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[1] Doubt has occasionally been thrown on the possibility of distinguishing a true yeast or a torula from an oidium or a degeneration form of some higher fungus by mere examination of the tissues. In the case of certain organisms which do not produce especially characteristic pathological effects, and are sufficiently similar morphologically, this may be true, but in the case of the three organisms

For all points of difference in the types of disease studied, we refer to the summary on page 60 and to the table on page 79.

As we have shown (page 60), the term blastomycosis has resulted in confusion of different diseases in the past and will continue to do so if used in the future, on account of its insufficient biological significance. Oidiomycosis is the proper name for the diseases occurring near Chicago and caused by the organisms budding in tissues and producing mycelium in cultures. Torula infection, coccidioidal granuloma, and yeast infection sufficiently designate the other diseases studied.

We wish to express our thanks to Dr. W. T. Councilman, as the instigator and constant helper and advisor in the work; to Dr. Harvey Cushing, for permission to use the cases; to Dr. S. B. Wolbach, for the cultures of the organisms and for many useful suggestions; to Dr. L. Frothingham, for the use of slides and tissue from his original case; to Dr. F. B. Mallory, for the use of slides; and to Dr. Roland T. Thaxter, for his careful examination of the organisms.

we studied there were no lesions where confusion as to the cause could exist after careful examination. Each variety of organism had a characteristic appearance in the tissues. When the histology and the distribution of the lesions are also considered, enough factors exist to make full identification possible. Lesions (not described in this paper) were also produced with various oidia (*Oidium albicans* and others, isolated from human throat infections), and no appearance was seen which would be confused with any of our other lesions. Reported cases of higher fungus infection in which budding forms occur in tissues are distinct from our cases. If we had had no cultures from the cases and no culture of torula from other sources for experimental purposes the nature of the organisms could not have been stated positively. In future other forms of torulæ or yeasts may be found which are not sufficiently characteristic in their effects to be distinguished from budding forms of higher fungi by histological examination alone. The cases described in this paper are probably a small part of those existing in nature and not yet studied. Thus, Escomel's recently reported cases of surface infection with budding organisms occurring in Peru and Bolivia are apparently caused by another variety of either yeast or torula. No mycelium is ever produced; the presence or absence of ascospores is not noted, and no plates are given or details of histology. The classification in this paper does not pretend to be complete, but merely to prevent confusion and to make clear the distinctions possible at the present time.

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X. EXPLANATION OF PLATES.

Plate 1.

Fig. 1. Slight atrophy and pitting of convolutions of the frontal lobe of the first case.

Fig. 2. Lesion in the frontal lobe of the first case.

Fig. 3. Cerebellar lesion in the first case.

Plate 2.

Fig. 4. Periphery of cerebellar lesion in the first case, showing the method of extension by solution of tissue. Stained with eosin and methylene blue. × 150.

Fig. 5. A group of intracerebral perivascular lesions in the first case. Stained with eosin and methylene blue.

Fig. 6. Single perivascular lesion in the first case. Stained with eosin and methylene blue. × 150.

PLATE 3.

FIG. 7. Small intracerebral lesion in the first case. Apparently the organisms arose from the large organism in the center. The drawing out of the secretion into threads is evident. Stained with eosin and methylene blue. × 2,000.

FIG. 8. Peripheral gliosis in the first case. Stained with phosphotungstic acid hematoxylin. × 1,000.

FIG. 9. Organisms in giant cells in the meninges in the first case. Cresyl blue stain. × 850.

PLATE 4.

FIG. 10. Granulation tissue filling the aqueduct of Sylvius in the first case. × 60.

FIG. 11. Area of meninges in the first case where the pseudotuberculous process is marked. Stained with eosin and methylene blue. × 100.

FIG. 12. Cerebellar lesions in the second case.

PLATE 5.

FIG. 13. Edge of cerebellar cortex showing meningitis in the second case. Stained with eosin and methylene blue. × 100.

FIG. 14. Organisms in meninges in the second case. Note the budding organism. Oil immersion. Stained with eosin and methylene blue. × 1,200.

FIG. 15. Lymph node in the second case. At the upper right hand corner is the edge of a mass of dense connective tissue. Stained with eosin and methylene blue. × 100.

FIG. 16. Lung lesion in the second case. Stained with eosin and methylene blue. × 100.

FIG. 17. Lesion in the internal capsule in the second case. Stained with hematoxylin and eosin. × 50.

FIG. 18. At the left side is the necrotic center of the lesion in Fig. 5. Oil immersion. Stained with hematoxylin and eosin. × 1,200.

PLATE 6.

FIG. 19. Giant cell containing organisms in the meninges in the second case.

FIG. 20. Organisms in a large vacuole in a meningeal giant cell of the second case.

FIG. 21. Meninges of a mouse infected intraperitoneally with a culture of ventricular fluid of the second case. Stained with hematoxylin and eosin. × 250.

FIG. 22. Radiating threads in an organism from Fig. 3. Oil immersion. Stained with hematoxylin and eosin. × 2,000.

FIG. 23. Radiating threads in organisms in cerebellar lesion in the first case. Cresyl blue stain. × 1,000.

FIG. 24. Original torula infection in the lung of a horse. Stained with hematoxylin and eosin. × 300.

FIG. 25. Intracerebral lesions in a rat infected intraperitoneally with torula.

FIG. 26. Torulæ in experimental lesion. Oil immersion. Stained with eosin and methylene blue. × 1,000.

FIG. 27. Torulæ in an endothelial cell in the lung of a rat. Oil immersion. Stained with eosin and methylene blue. × 2,000.

PLATE 7.

FIG. 28. Torula lesion in a rat infected intraperitoneally. Stage of healing. Stained with eosin and methylene blue. × 150.

FIGS. 29, 30, 31. Torulæ in experimental lesions. Oil immersion. Note the apparent nucleus in Fig. 31. × 2,000.

FIG. 32. Budding torulæ. Note the extremely small buds. Oil immersion. Stained with eosin and methylene blue. × 1,000.

FIG. 33. Variations in the size of torula in an experimental lesion in a rat (lung). Oil immersion. Stained with hematoxylin and eosin. × 2,000.

FIG. 34. Meningeal lesion in a rat infected intraperitoneally with torula. × 2,000.

FIG. 35. Pseudotuberculous lesion in a peritoneal nodule in a rat infected with torula. Note organisms in spaces. Stained with eosin and methylene blue. × 50.

FIG. 36. Lesions like miliary tubercles in the lung of a rat infected with torula by heart injection. Stained with eosin and methylene blue. × 50.

PLATE 8.

FIG. 37. Organisms in a destroyed giant cell in the meninges in the second case. At the upper left hand corner are two red blood corpuscles for comparison of size. Camera lucida drawing. Oil immersion. Mallory's aniline blue connective tissue stain.

FIG. 38. Beginning lesion in a meningeal giant cell in the second case. The organisms are thinner walled than in Fig. 1. Camera lucida drawing. Oil immersion.

FIG. 39. Organisms in the meninges of a mouse infected intraperitoneally with a culture of ventricular fluid of the second case. Note budding of the small organism. Camera lucida drawing. Oil immersion.

PLATE 9.

FIG. 40. Organisms in a giant cell in the lung of a rat infected with torula. The central part of the cell contains the completely finished drawing. Camera lucida. Oil immersion.

FIG. 41. Organisms in the lung of a rat infected with torula. Camera lucida. Oil immersion.

FIG. 42. Very small torulæ in the cerebellar cortex of an infected rat. Camera lucida. Oil immersion.

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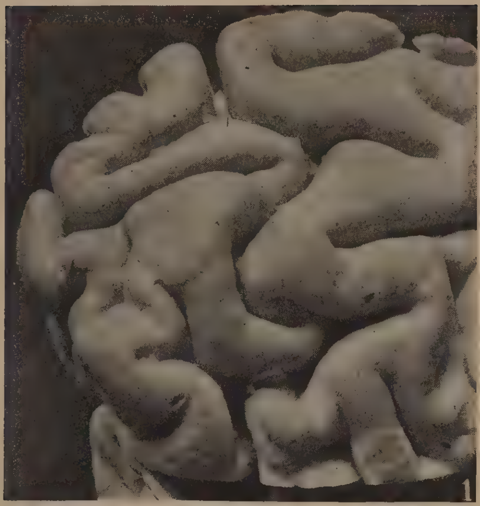

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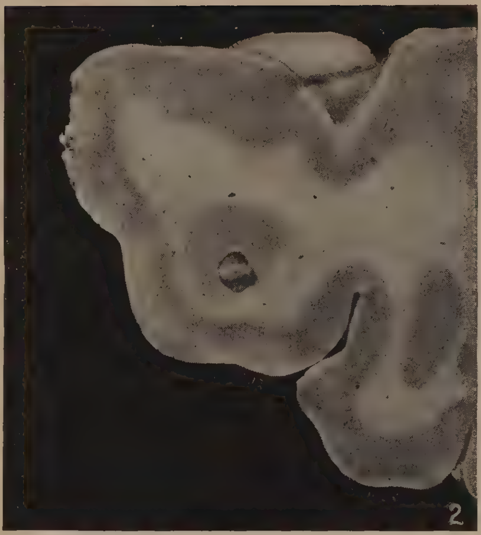

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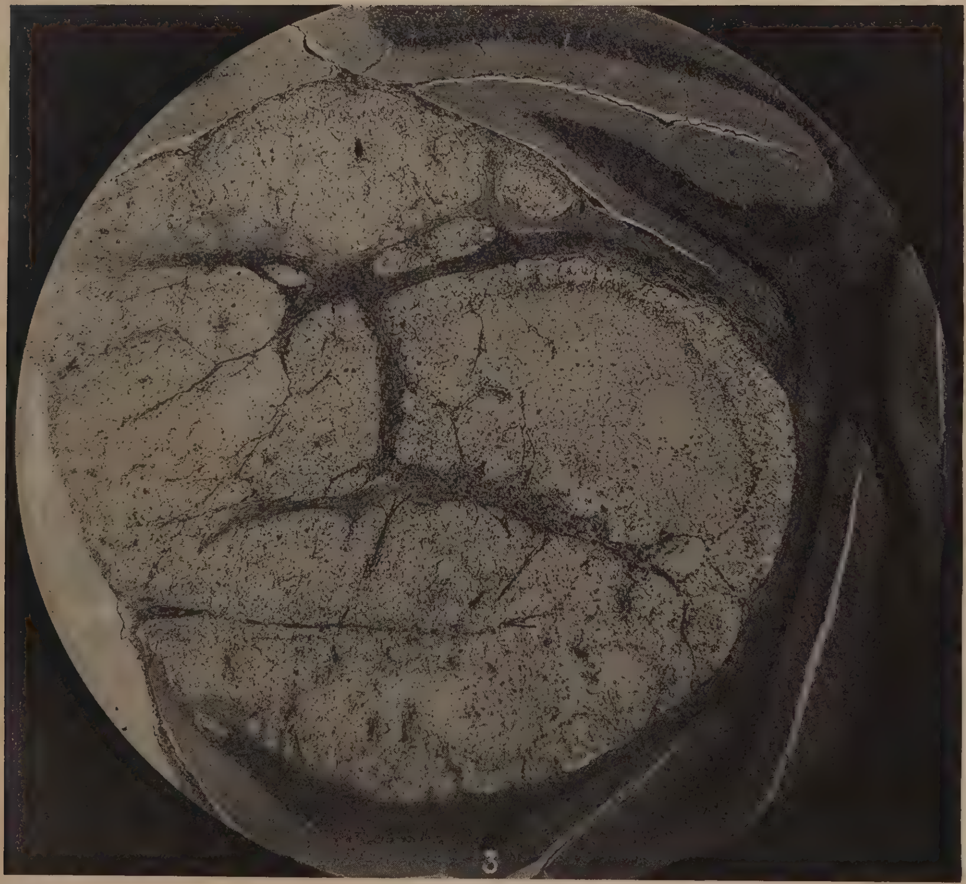

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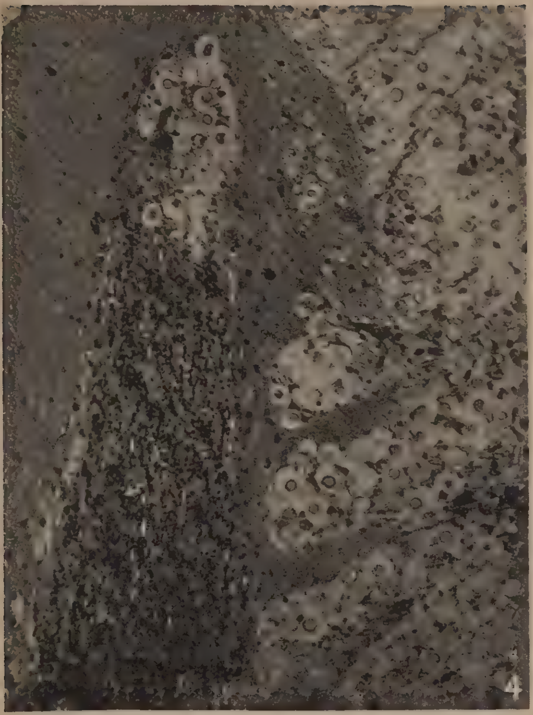

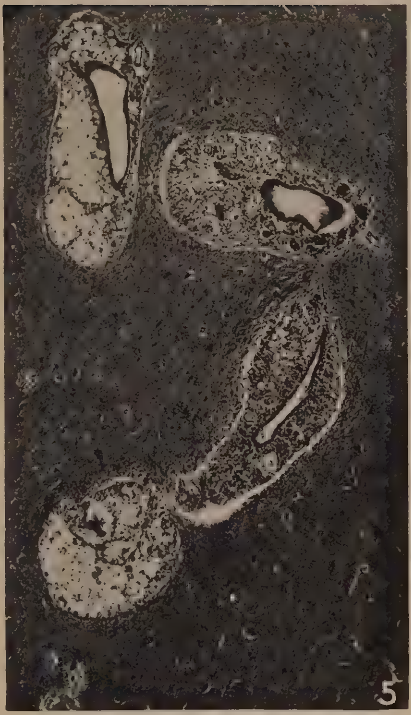

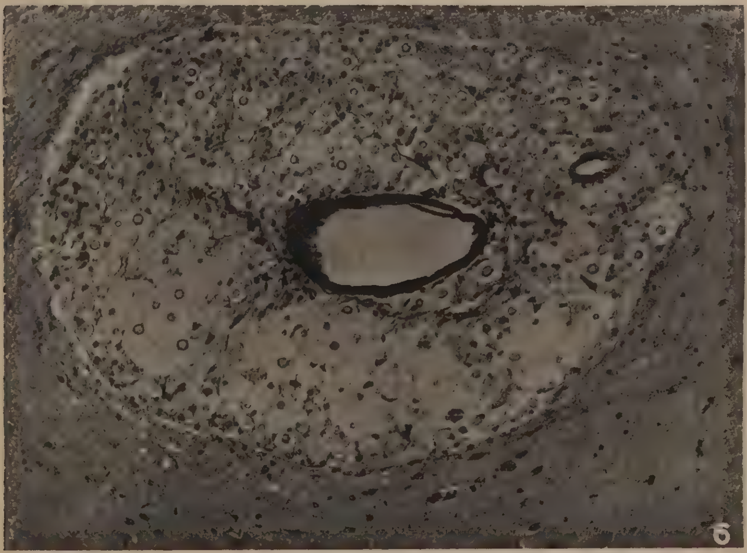

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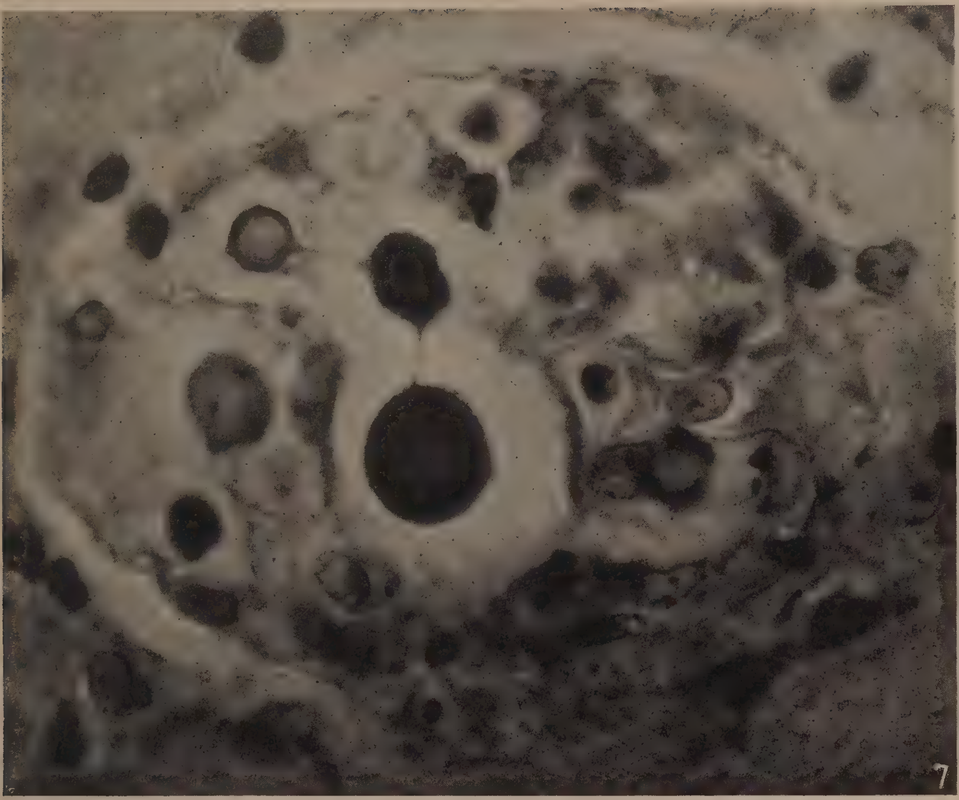

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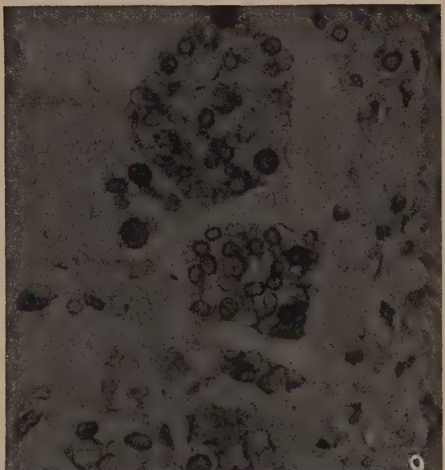

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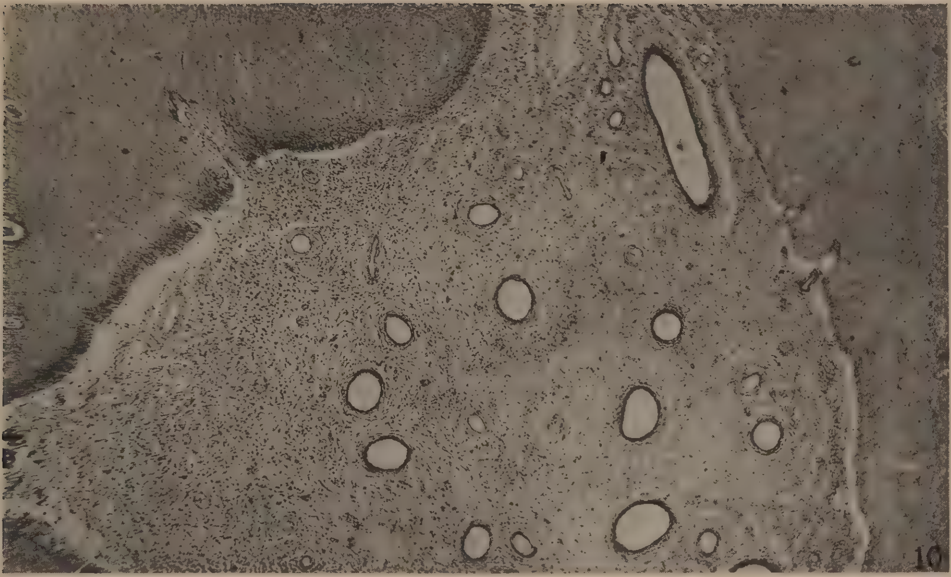

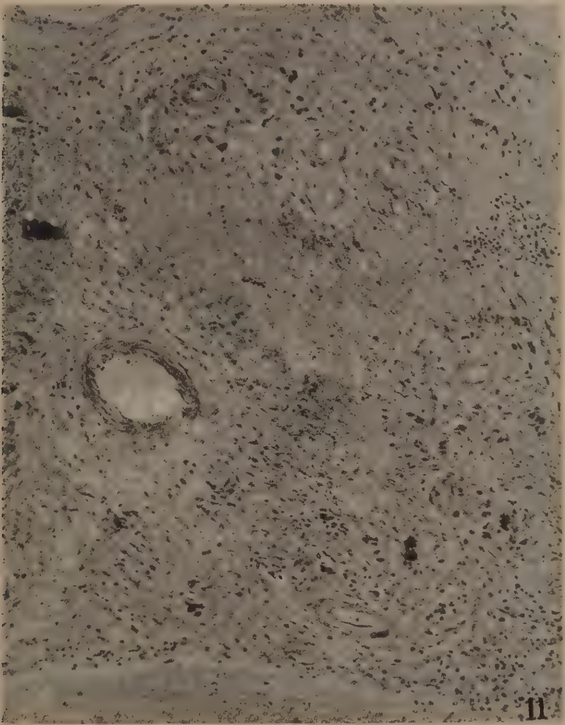

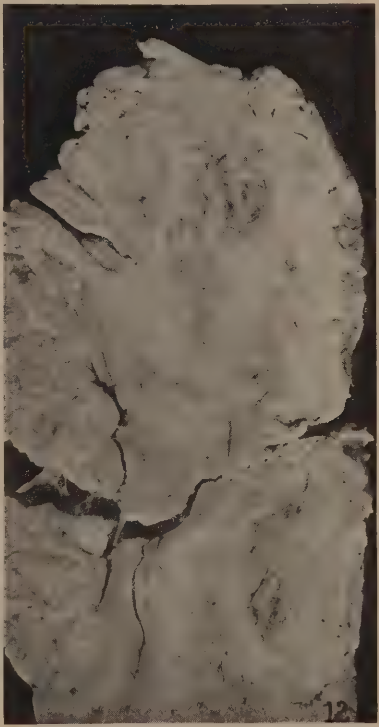

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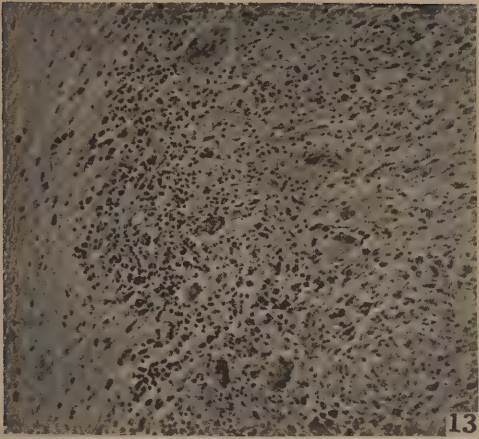

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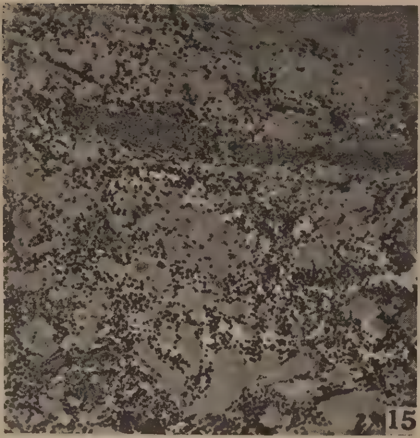

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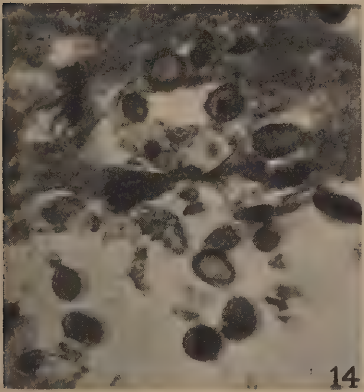

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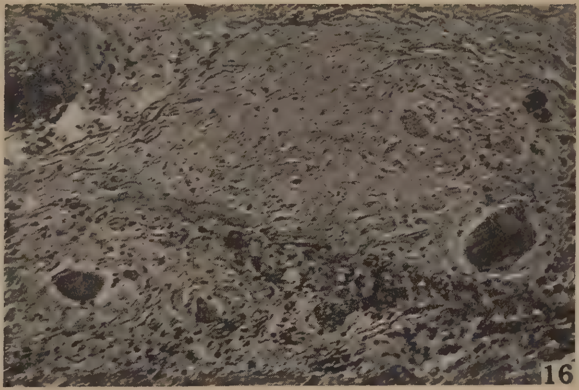

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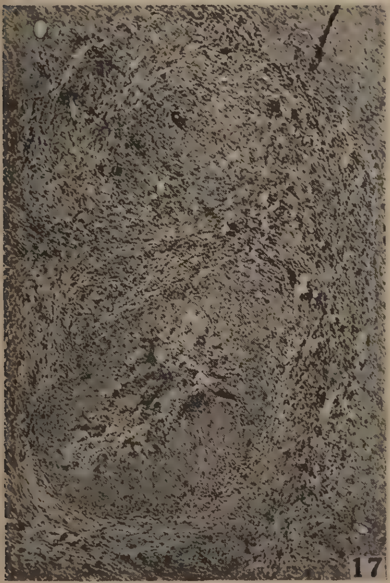

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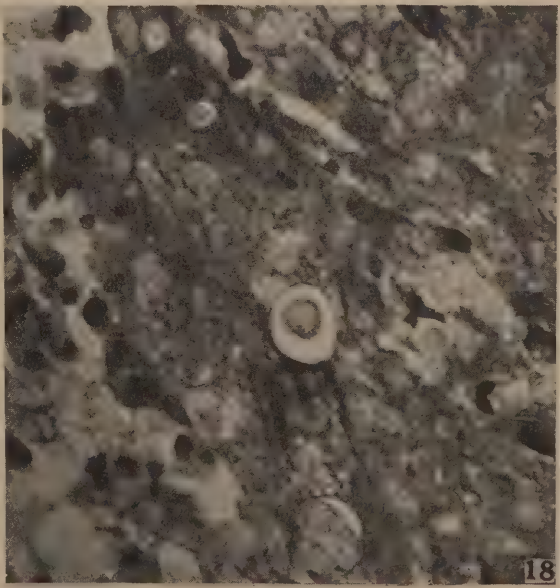

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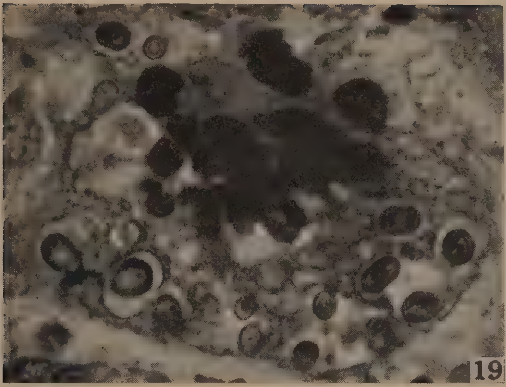
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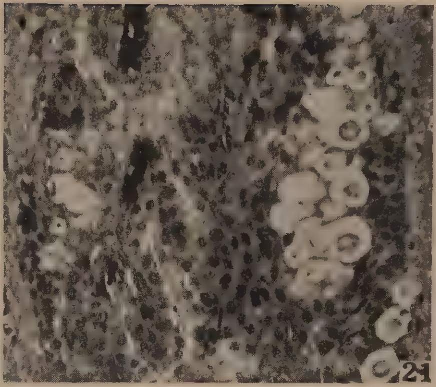
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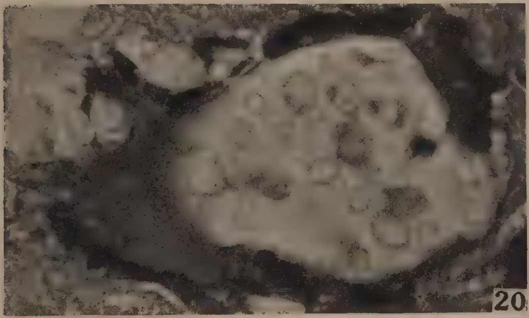
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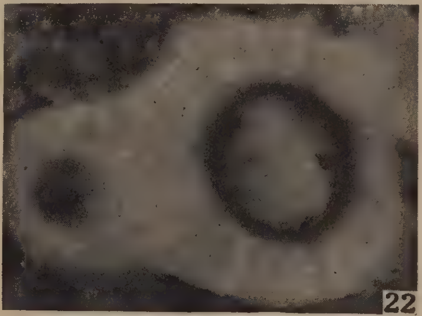
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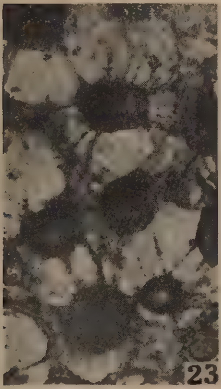
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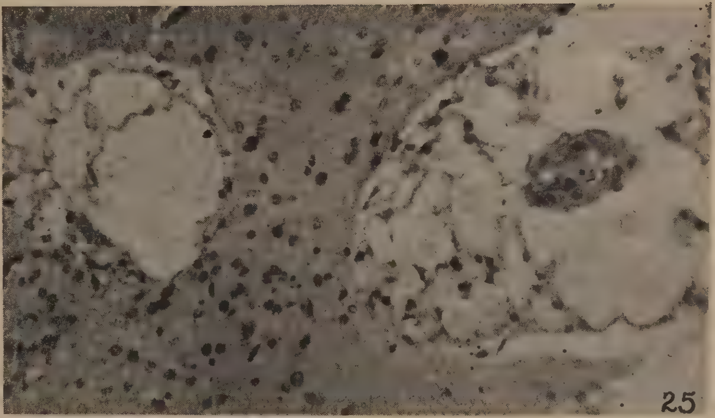
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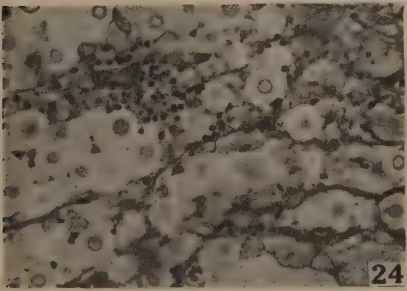
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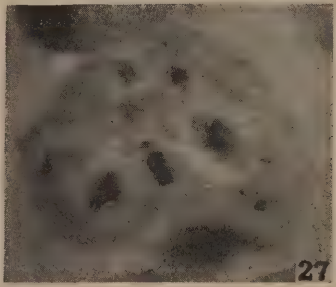
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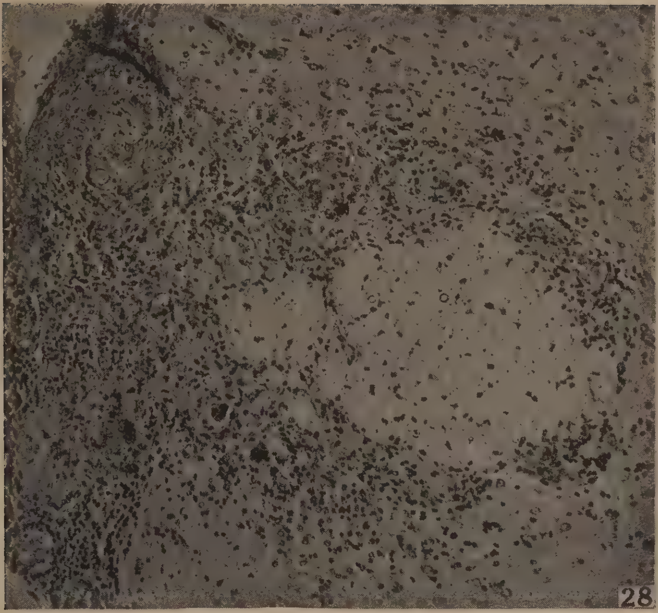
(Stoddard and Cutler: Torula Infection.)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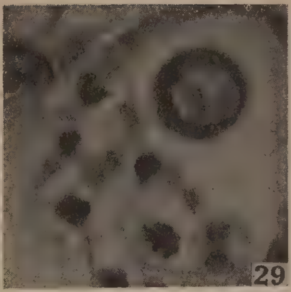
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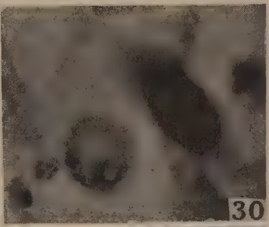
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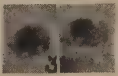
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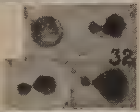
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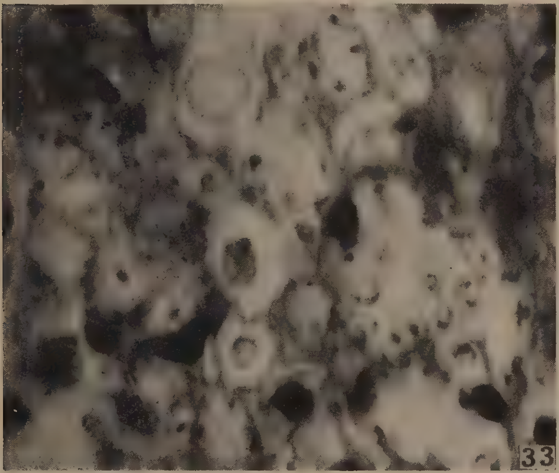
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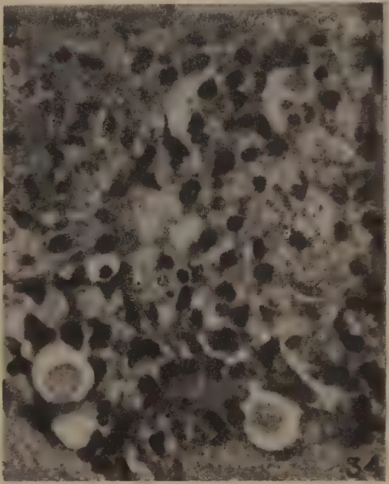
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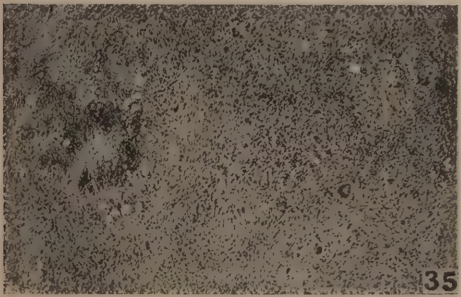
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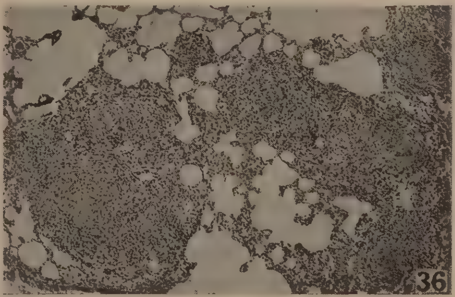
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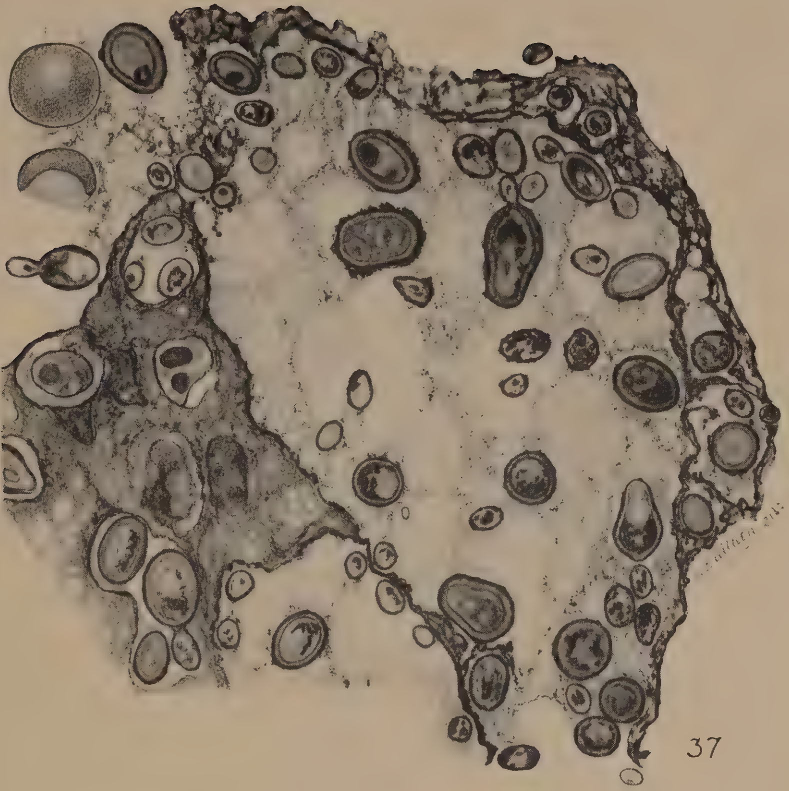
(Stoddard and Cutler: Torula Infection.)



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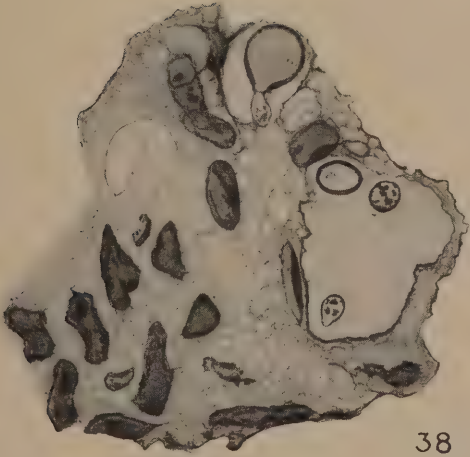

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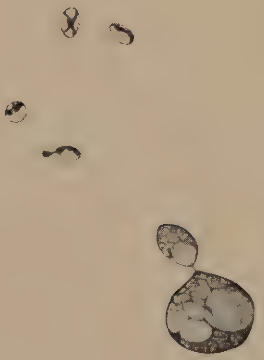

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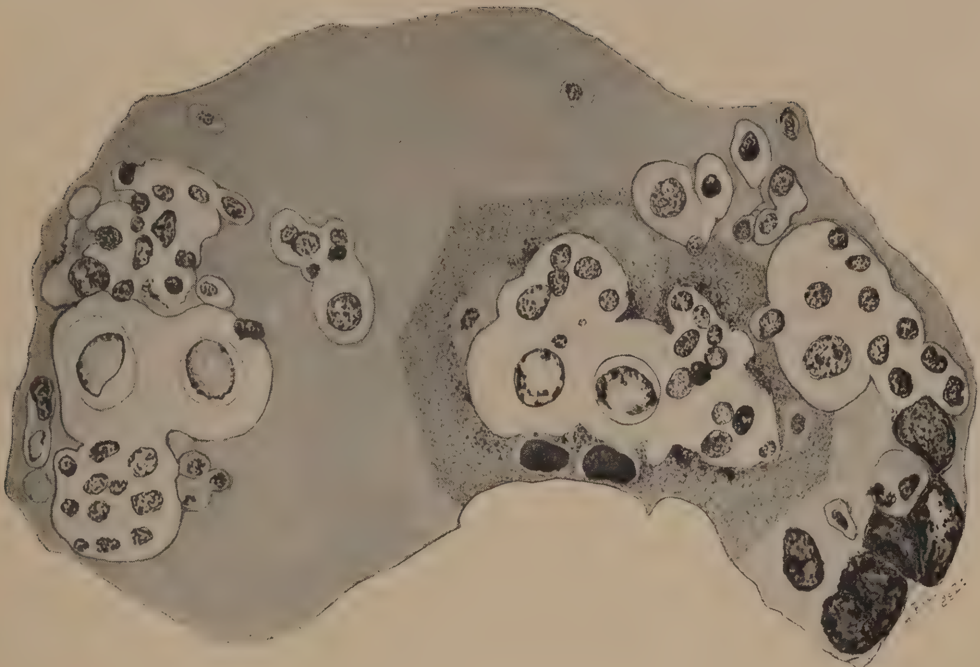
(Stoddard and Cutler: Torula Infection.)



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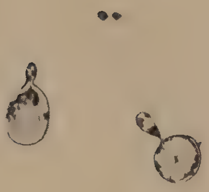

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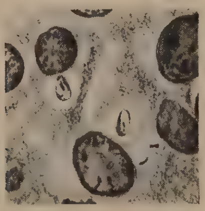

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